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PREPARATION AND PROPERTIES OF SELECTED ORGANIC SULFUR COMPOUNDS

by

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Preparation and Properties of Selected Organic Sulfur Compounds" submitted by Sharon Jean Matthias in partial fulfilment of the requirements for the degree of Master of Science.

R. T. Coutts
Supervisor

JAN 29 1970

Date.....

ABSTRACT

Derivatives of (o-nitrophenylthio)acetate were prepared by condensation of α-mercaptoacids with substituted o-chloro- or o-bromonitrobenzenes, followed by esterification of the products. The o-nitroesters so obtained underwent reductive cyclization using sodium borohydride and palladium-charcoal to yield derivatives of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine.

The action of aqueous hydrochloric acid and aqueous sodium hydroxide on these cyclic hydroxamic acids was studied. Many unexpected products were obtained. In the former case, attack of Cl^- occurred concomitantly with loss of the hydroxamate OH group to yield chlorinated lactams. Non-chlorinated lactams were also obtained in smaller yields. When aqueous sodium hydroxide was employed, loss of the hydroxamate OH group also occurred, yielding the corresponding lactam. Alterations in the side chain yielded derivatives of 3,4-dihydro-3-oxo-2H-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetic acid. Evidence for opening of the heterocyclic ring, followed by scission of the S-C bond was obtained in one case.

Compounds possessing an active methylene group were reacted with o-nitrobenzenesulfenyl chloride. The o-nitro-ketones and -β-ketoesters so produced were reduced using the sodium borohydride/palladium-charcoal system in an attempt to synthesize 2H-1,4-benzothiazine N-oxides. Reduction of the o-nitro-ketones produced compounds in which the ketone group had been reduced to the alcohol but

the nitro group was unaffected. Also, products which possessed both an alcohol and an amine grouping were obtained in smaller yield. When ethyl α-benzoyl-α-(o-nitrophenylthio)acetate was reduced using this system, a variety of products were obtained. In the formation of one product, hydrolysis and decarboxylation occurred, resulting in the loss of the ethoxycarbonyl group. In another, the ethoxycarbonyl group was retained and the nitro group was reduced to a hydroxylamine, as evidenced by the isolation of a hydroxamic acid. Use of excess palladium-charcoal catalyst in the reducing medium yielded several interesting products. Some cyclic product was isolated in all cases and evidence for the formation of cyclic N-oxides or N-hydroxy compounds was obtained.

Attempts to prepare derivatives of cyclic benzothiazine hydroxamic acids using xanthdrol were only partially successful.

ACKNOWLEDGMENTS

The author wishes to express her deep gratitude to Dr. R.T. Coutts, without whose patience and assistance this thesis could not have been completed.

Also, to her mother and to her husband, for their faith and understanding.

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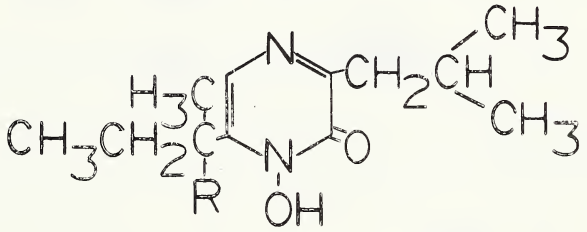
INTRODUCTION

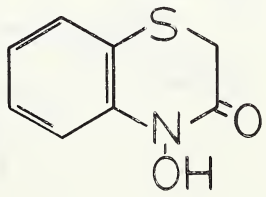
Since the isolation of aspergillic acid (Ia) in 1940 from Aspergillus flavus, and the discovery of its high in vitro antibacterial activity against both Gram-positive and Gram-negative organisms, an increasing interest has been shown in cyclic hydroxamic acids. Some compounds containing the hydroxamic acid grouping occur naturally, while others have been synthesized. Many show a wide range of very interesting pharmacological properties, and have been the subject of a recent review (1).



I

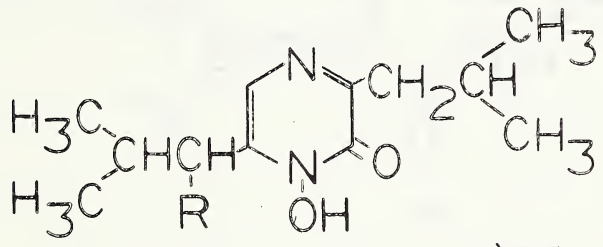
a) R = H
b) R = OH

The present investigation is concerned mainly with the preparation and properties of derivatives of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (II), and so only compounds with some structural similarity to II will be discussed here.



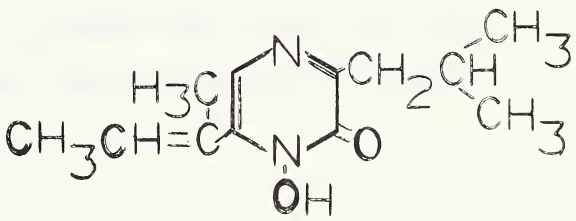
II

The antimicrobial activities of aspergillic acid (Ia) and its analogs neoaspergillic acid (IIIa), hydroxyaspergillic acid (Ib), neohydroxyaspergillic acid (IIIb), dehydroaspergillic acid (IV), and tetrahydroaspergillic acid (V) have been compared (2, 3). The results indicated that aspergillic acid, neoaspergillic acid, and dehydro-

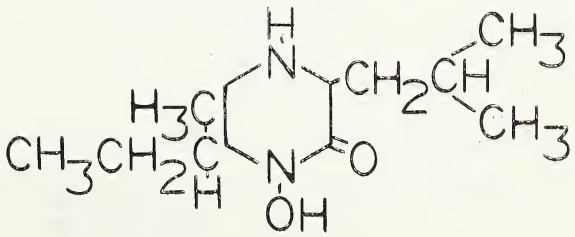


III

a) R=H
b) R=OH

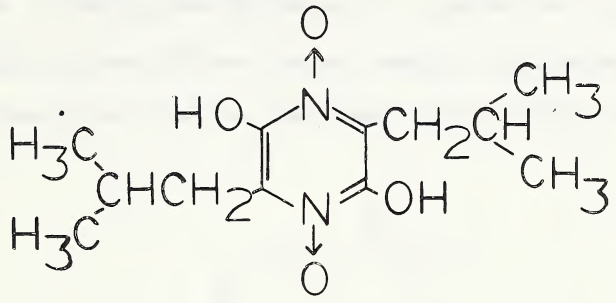


IV



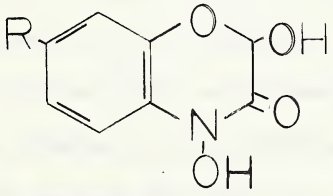
V

aspergillic acid showed more inhibitory effect than the others on certain selected organisms. The related compound, pulcherriminic acid (VI) (4), also possesses antibacterial properties (5).



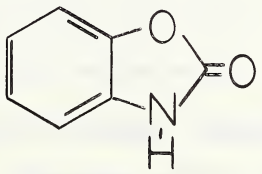
VI

3,4-Dihydro-2,4-dihydroxy-3-oxo-2H-1,4-benzoxazine (VIIa) and its enzymatic decomposition product, 2(3)-benzoxazolinone(VIII), possess antifungal and antibacterial properties(6). Both compounds were isolated from rye seedlings by Honkanen and Virtanen (7). The benzoxazine (VIIa) is present in the seedlings as the glucoside.



VII

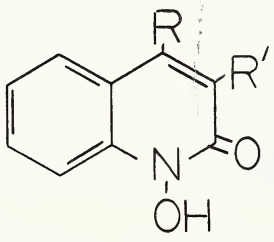
a) R = H
b) R = OCH_3



VIII

The related compound 3,4-dihydro-2,4-dihydroxy-7-methoxy-3-oxo-2H-1,4-benzoxazine (VIIb) (Dimboa) is an antimetabolite. It has been isolated from corn and other grass seedlings (8).

Coutts, Pitkethly and Wibberley (5) synthesized quinolones of general formula IXa and IXb and tested them for antibacterial activity in vitro. They found that the hydroxamic acid grouping by itself did



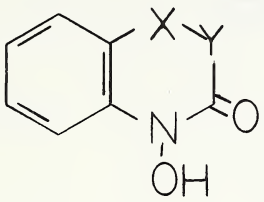
IX

a) R = OH
b) R = H

not confer antibacterial properties, but that the nature of the side chain also had some effect on the activity of the compounds. The most active compounds had a methyl, ethyl, iso-propyl, or iso-butyl substituent in the 3-position.

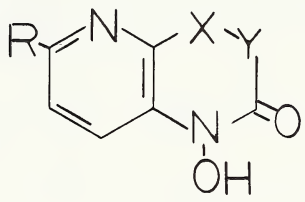
Coutts, Noble and Wibberley (9) also prepared compounds of general formula X, XI and XII and tested them for antibacterial activity against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Salmonella typhi and Proteus vulgaris. Observed activity was compared to that of 1,2-dihydro-1-hydroxy-2-oxoquinoline (Xa), a known antibacterial agent (10). None of their compounds showed general activity comparable to that of Xa.

Compounds of general formula XIII have been synthesized and tested for their antibacterial activity against Escherichia coli and Staphylococcus aureus (11) since XIIIa had been shown to possess some antibiotic properties (9). Results were disappointing however. Com-



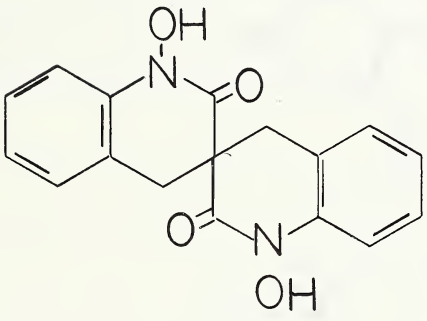
X

a) X-Y = CH=CH
b) X-Y = CH_2-NH
c) X-Y = O-CH_2

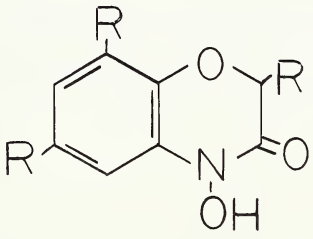


XI

a) R=H; X-Y = NH-CH_2
b) R=Me; X-Y = N=C(OH)



XII

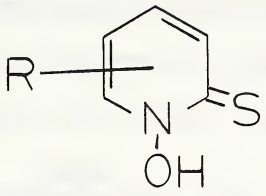


XIII

a) R=R' = R'' = H
b) R=Me; R' = R'' = H
c) R=Et; R' = R'' = H
d) R= n-Bu; R' = R'' = H
e) R' = Cl; R=R'' = H
f) R=R' = Me; R'' = H

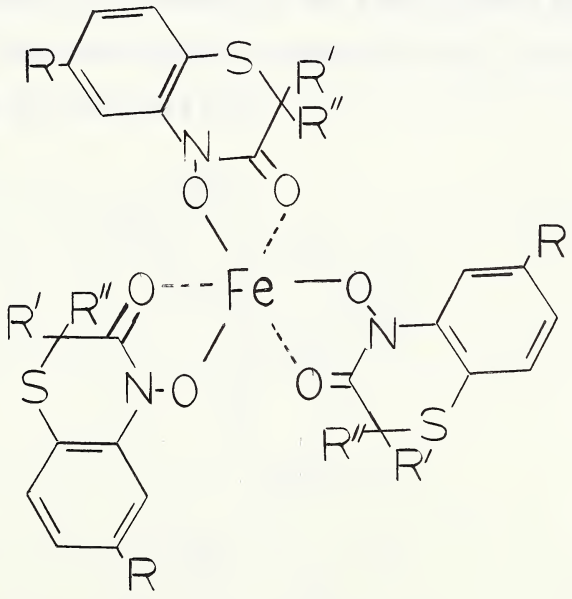
pounds XIIIb-XIIIf were shown to be inactive against these organisms at a concentration of 40 mg. per cent.

Cyclic thiohydroxamic acids of general formula XIV are also known (12) to exhibit high in vitro antibacterial activity.



XIV

The antibacterial activity of hydroxamic acids can be attributed to their ability to chelate with metals. Characteristic of the



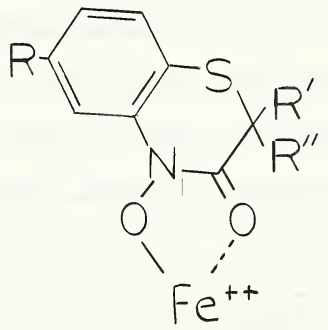
XV

hydroxamic acids is the formation of a deep wine to purple color which appears upon addition of an ethanolic solution of ferric chloride. Studies have shown that the structure of the ferric chelate is dependent both on the quantity of iron present and on the pH of the solution.

The visible absorption spectrum of each of the three soluble complexes of benzohydroxamic acid differs (13).

pH	Color	Ratio Fe:Benzohydroxamic acid	Max.
1	purple	1:1	510 mμ
3.5	red	1:2	480 mμ
3.5	yellow-red	1:3	440 mμ

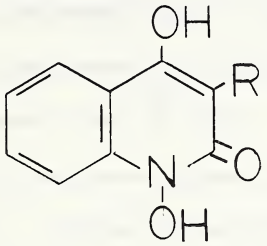
The yellow-red (1:3) complex of the benzothiazine hydroxamic acids, therefore, has been assigned structure XV (14), and the purple (1:1) complex has the structure XVI.



XVI

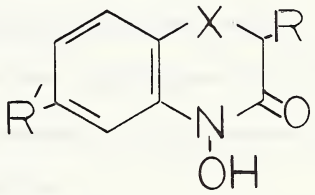
Cyclic hydroxamic acids have also been shown to reactivate diisopropylphosphofluoridate (DFP)-inhibited acetylcholinesterase

(15). Compounds of general formula IXa and XVII showed 0.44-2.25 times the activity of pyridine-2-aldoxime methiodide (PAM) which is a well-known reactivator of organophospate-inhibited cholinesterase and an effective antidote against insecticide poisoning.



IXa

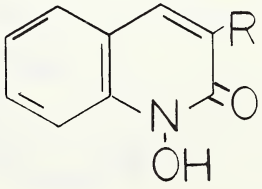
i) R = H
ii) R = CN



XVII

a) X = S; R = R' = H
b) X = S; R = Me; R' = H
c) X = S; R = CH_2COOCH_3; R'=Br
d) X = SO_2; R = R' = H
e) X = O; R = R' = H

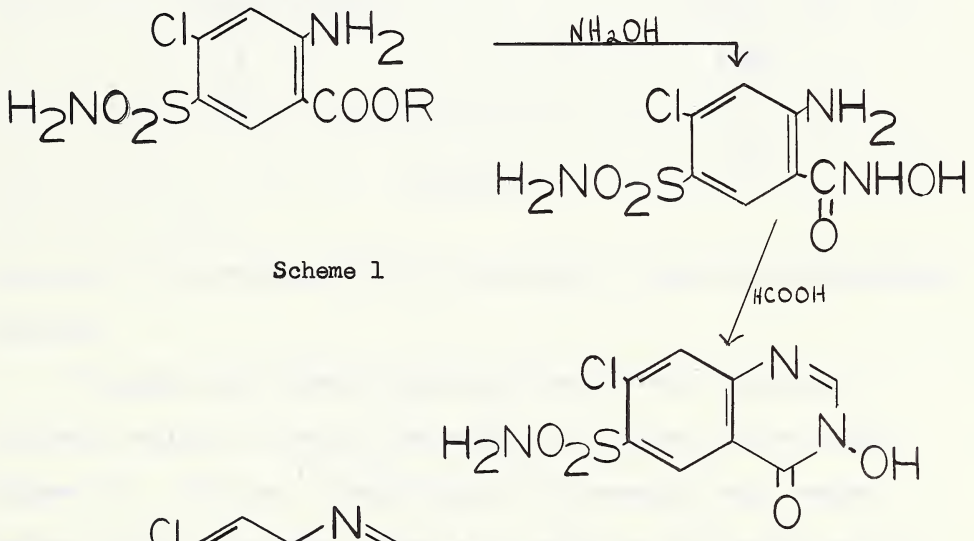
Preliminary screening indicated that cyclic hydroxamic acids of general formula IXb might show hypnotic properties. In tests on mice, it was found (5) that 3-ethyl-1,2-dihydro-1-hydroxy-2-oxoquinoline (**IXb**, R = Et) had a hypnotic effect at concentrations of one-eighth of



IXb

the LD_{50} dose. When other compounds of this general formula were tested, however, (IXb; R = Me, n-Pr, iso-Pr, n-Bu, and iso-Bu), the concentration required to produce a hypnotic effect was too close to the LD_{50} dose. The authors concluded that the hypnotic effect was simply a measure of the compounds' toxicity.

The hydroxamic acid, 7-chloro-3,4-dihydro-3-hydroxy-4-oxo-6-sulfonamidoquinazoline (XVIII) is structurally similar to the diuretic agent Diuril® (XIX). The former was synthesized (16) from an ester of 2-amino-4-chloro-5-sulfonamidobenzoate in the manner shown. (Scheme 1). It also shows diuretic properties.



Scheme 1

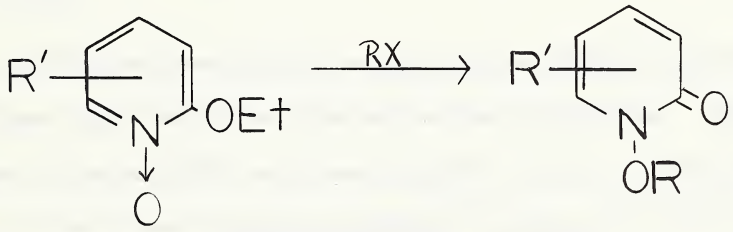
XVIII

XIX

Diuril®

Alkyl, alkenyl or aryl derivatives of hydroxamic acids also

exhibit pharmacological properties. Paquette has done work in this field (17, 18, 19, 20). Treatment of a pyridine-1-oxide with a suitable halide yielded compounds with a general formula XX (Scheme 2). When R was a 2-alkenyl substituent, e.g. allyl or 2-octenyl, the compounds exhibited sedative and muscle relaxant properties and also were useful in the treatment of topical fungal infections. When pyridine-1-oxides were treated with a cycloalkyl halide, e.g. cyclopentyl or



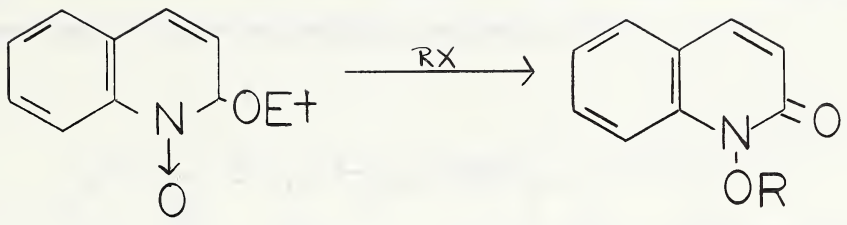
XX

Scheme 2

cyclooctyl, the products (XX; R = cycloalkyl), showed antiinflammatory activity.

Paquette also treated quinoline-1-oxides with benzyl and 2-alkenyl halides to produce compounds with a general formula XXII (Scheme 3). If R was a benzyl group, the compounds were central nervous system stimulants. They also exhibited antifungal activity against certain microorganisms which attack animals and plants.

Treatment of 2-alkoxyquinoline-1-oxides with a 2-alkenyl halide gave compounds which were sedatives, anticonvulsants and muscle relaxants. They also exhibited antiinflammatory activity against

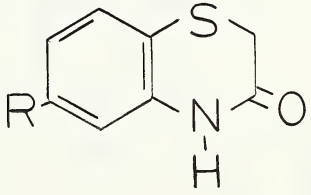


XXI XXII

Scheme 3

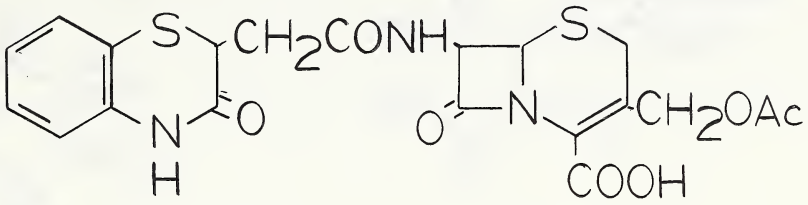
various fungi.

3,4-Dihydro-3-oxo-2H-1,4-benzothiazines (XXIII) and their derivatives also show varied pharmacological properties. Compounds of general formula XXIII have been prepared and show a paralysant effect on liver-fluke (Fasciola hepatica) in vitro (21, 22, 23). The unsubstituted compound, the 6-bromo and 6-chloro-derivative were the most effective.



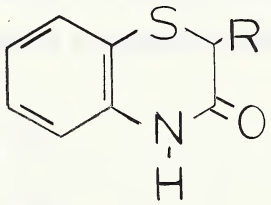
XXIII

A benzothiazine derivative of 7-aminocephalosporanic acid (XXIV) has been shown to have bactericidal properties (24).



XXIV

Many compounds of general formula XXV have been prepared and tested for antibacterial activity (25). Compounds XXVa, XXVb and XXVc show moderate activity against Trichophyton mentagrophytes, compounds XXVc and XXVd show marked phytotoxic activity against Chenopodium album and XXVe exhibits activity against Artemisia vulgaris.

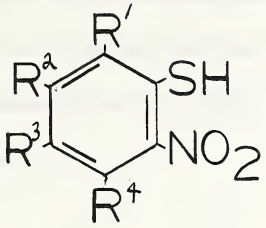


XXV

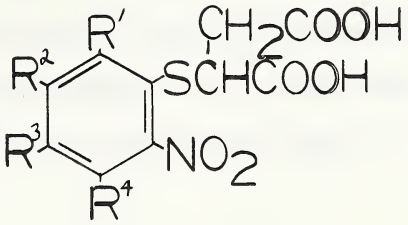
a) R = OAc
b) R = OBz
c) R = OBu
d) R = OC_5H_{11}
e) R = CH_2COOH

Bourdais (26) found (3,4-dihydro-3-oxo-2H-1,4-benzothiazine)-acetic acids and esters (XXVI) and their precursors, the thiophenols

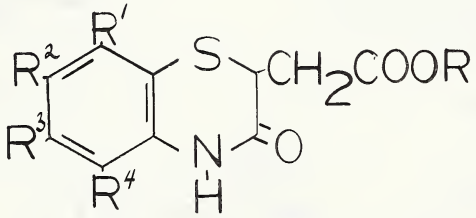
(XXVII) and phenylthiosuccinic acids (XXVIII) to be fungicides and herbicides.



XXVII



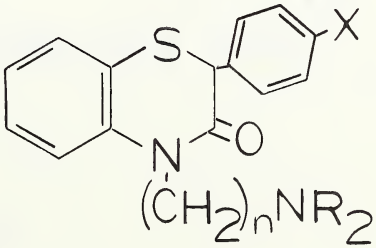
XXVIII



XXVI

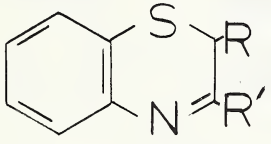
Spasmolytic and antihistaminic properties are shown (27, 28) by compounds of type XXIX (n = 2 or 3), and inhibition of tremor activity in Parkinson's disease is a property possessed by compounds of type XXX and their salts (29).

XXIX

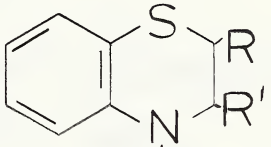


XXX

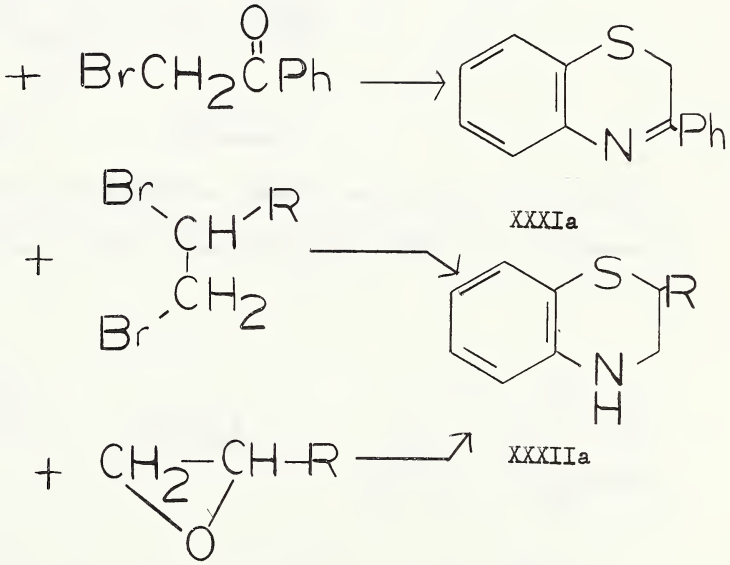
Preparation of substituted 2H-1,4-benzothiazines (XXXI) is achieved using either o-aminothiophenol or o-chloronitrobenzene as precursors (30, 31). o-Aminothiophenol will react with bromomethylketones, with derivatives of 2,2-dibromoethane, and with 1,2-epoxides (32) to form derivatives of 2H-1,4-benzothiazine, or 3,4-dihydro-2H-1,4-benzothiazine (XXII). Examples of these reactions are given in Scheme 4.



XXXI

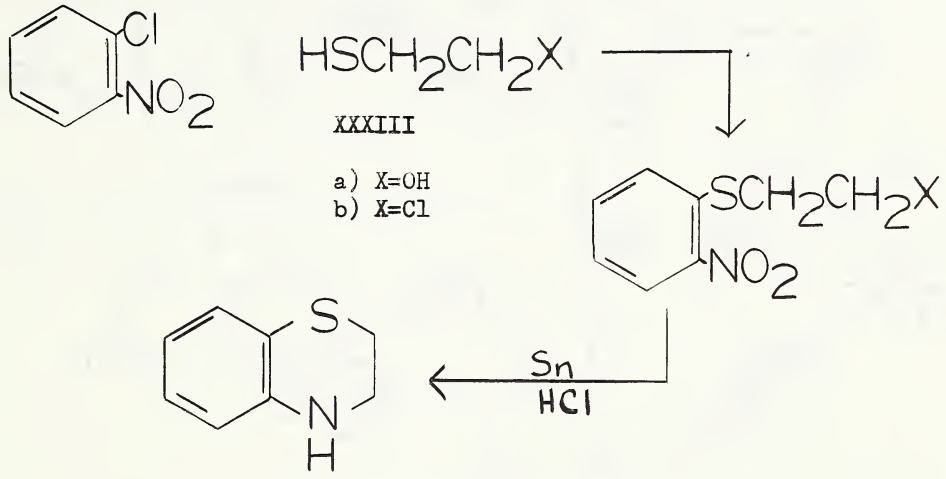


XXXIII



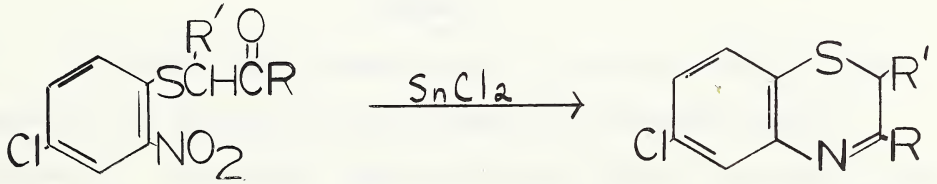
Scheme 4

o-Chloronitrobenzene condenses with β-hydroxyethyl mercaptan (XXXIIIa) or β-chloroethyl mercaptan (XXXIIIb) (31). Reduction of the product with stannous chloride yields 3,4-dihydro-2H-1,4-benzothiazine (XXXII, R = R' = H) (Scheme 5).



XXXII Scheme 5

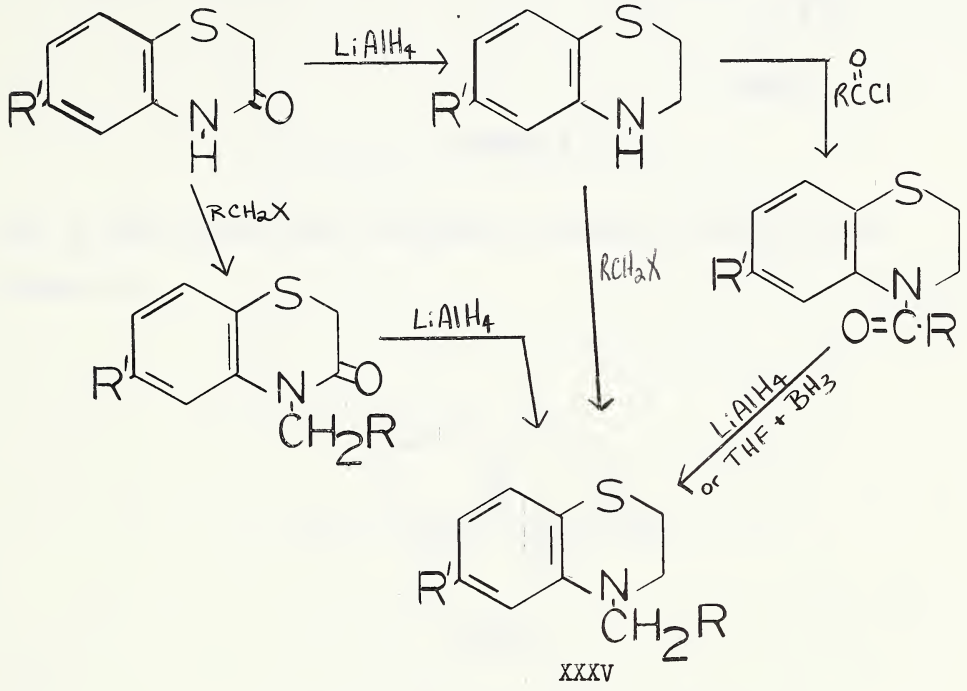
Reduction of o-nitrophenylthioketones (XXXIV) with stannous chloride also yields derivatives of 2H-1,4-benzothiazine (XXXI) (33) (Scheme 6).



XXXIV XXXI

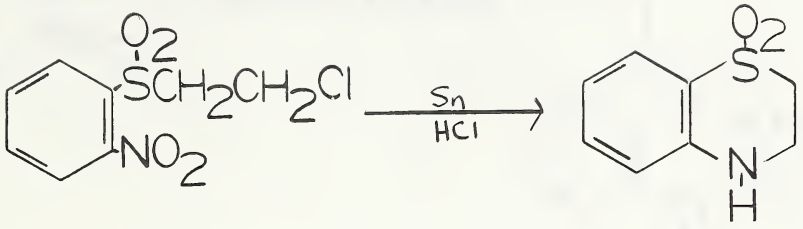
Scheme 6

Prasad and Tietje (34) synthesized 3,4-dihydro-2H-1,4-benzothiazines and their alkyl derivatives (XXXV) by reducing 3,4-dihydro-3-oxo-2H-1,4-benzothiazines or their alkyl derivatives with $LiAlH_4$ (Scheme 7).



Scheme 7

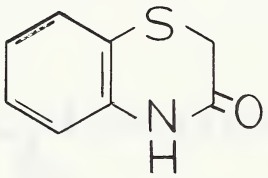
3,4-Dihydro-2H-1,4-benzothiazine 1,1-dioxide (XXXVI) is prepared (30) by reduction of o-nitrophenyl-β-chloroethylsulfone (Scheme 8). The related 3-oxo-derivative, XXXVII, is prepared by condensation of o-aminothiophenol with bromoacetic acid (35), or by reduction of (o-nitrophenylthio)acetic acid (36). o-Aminothiophenol will condense with compounds such as glycidic esters, (32), ethyl cinnamate (37), maleic acid (37), and acetylene dicarboxylic acid



XXXVI

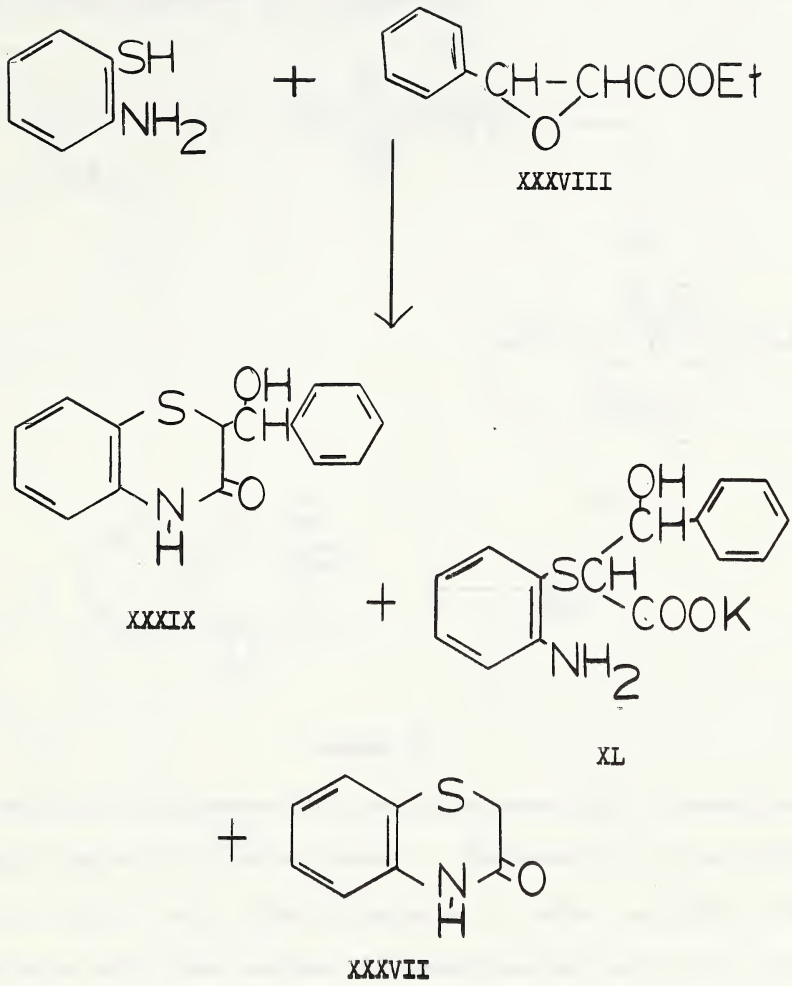
Scheme 8

(38) to yield substituted 3,4-dihydro-3-oxo-2H-1,4-benzothiazines (Scheme 9).



XXXVII

In the case of glycidic esters (32), ring closure takes place on the ester group in preference to the hydroxyl group (Scheme 10). If the ester is hydrolyzed before ring closure occurs, no reaction takes place. Condensation of ethyl phenylglycidate with o-aminothiophenol produces a mixture of (3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)phenylethanol (XXXIX), potassium β-hydroxy-α-(o-aminophenylthio)-β-phenylpropionate (XL) and 3,4-dihydro-3-oxo-2H-1,4-

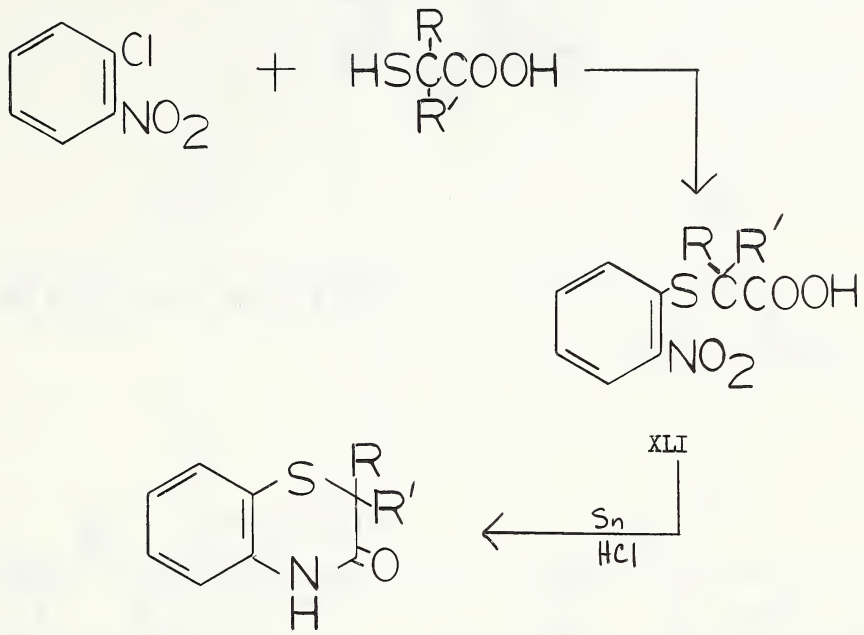


Scheme 10

benzothiazine (XXXVII). The potassium salt XL is converted to the lactam XXXIX on acidification but is easily converted to XXXVII by warming with dilute alkali.

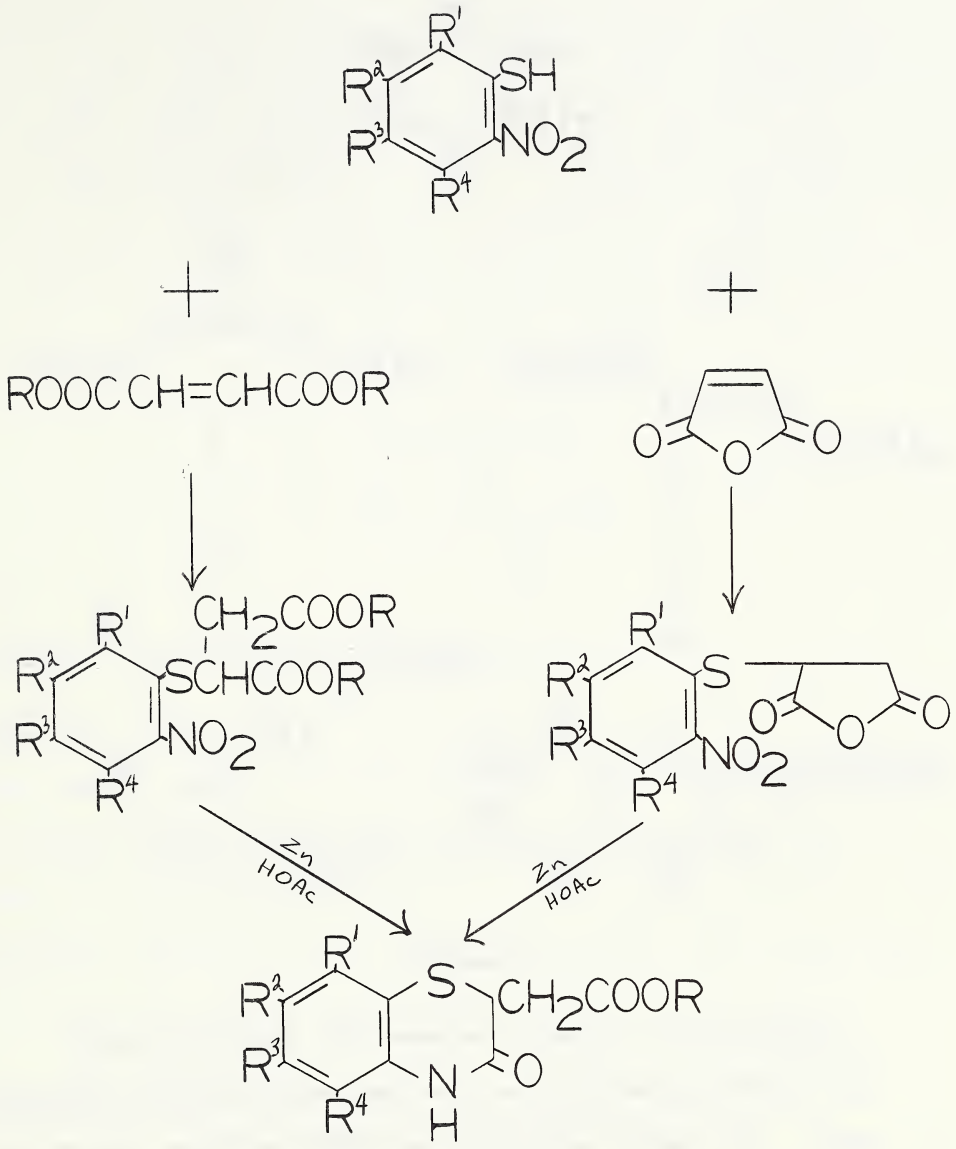
Condensation of o-chloronitrobenzene with mercaptoacids and reduction of the resulting product (XLI) also yields 3,4-dihydro-3-

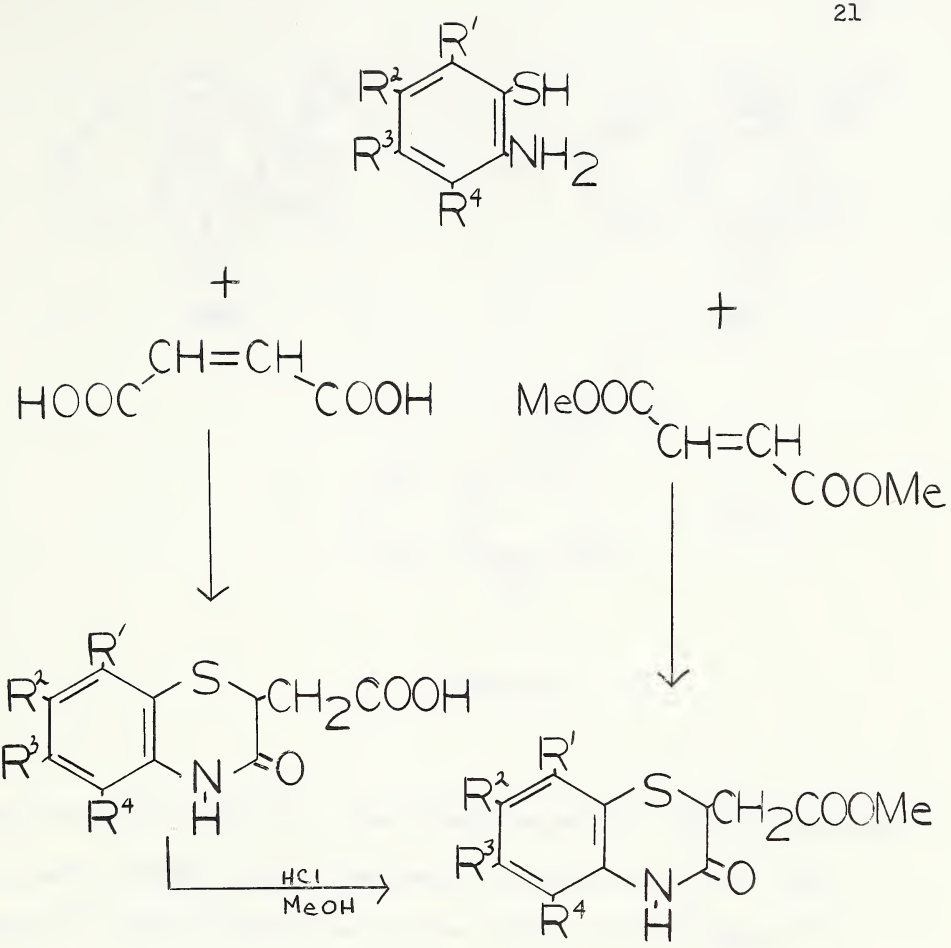
oxo-2H-1,4-benzothiazines (30) (Scheme 11).



Scheme 11

Bourdais (26) prepared (3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acids in a similar manner. Condensation of o-nitrothiophenol with maleic acid, dimethyl maleate, or maleic anhydride yielded intermediates which were reduced to benzothiazines using zinc and glacial acetic acid (Scheme 12). Condensation of o-aminothiophenol with maleic acid or methyl fumarate also yielded (3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acids or acetates (Scheme 13).

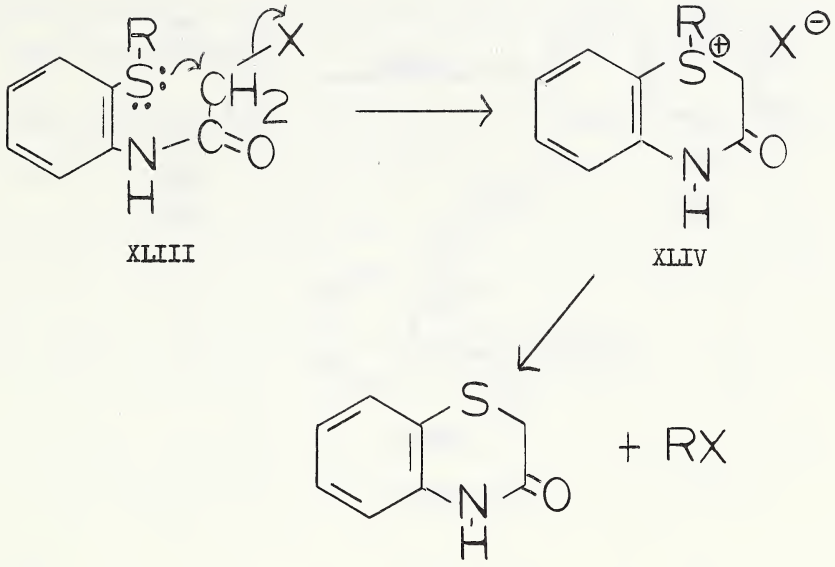

R1
R2
R3
R4
SH
NO2
ROOC CH=CHCOOR
O
O
O
CH2COOR
SCHCOOR
S
Zn
HOAc
Zn
HOAc
CH2COOR
N
H



Scheme 13

Prasad and Tietje (34) reported formation of 3,4-dihydro-3-oxo-2H-1,4-benzothiazine when 2-(α-chloracetamide)phenylalkyl (and aralkyl) sulfides (XLIII) were distilled (Scheme 14). They suggested a 6-membered cyclic sulfonium halide (XLIV) as intermediate.

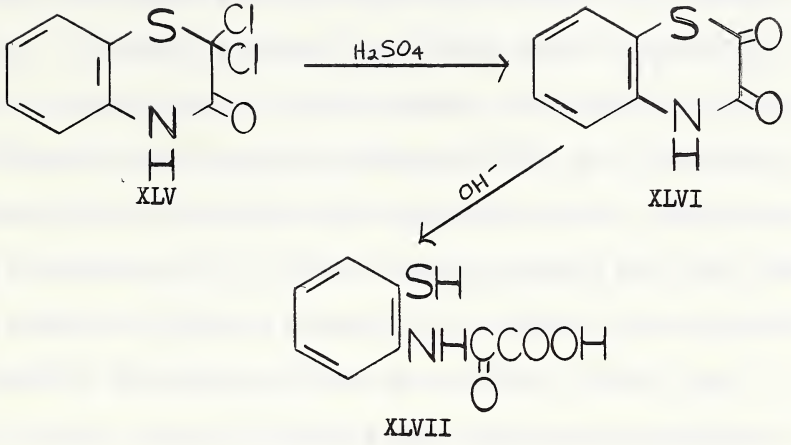
The methylene group in the 2-position of 3,4-dihydro-3-oxo-2H-1,4-benzothiazine has 2 active hydrogen atoms. One is easily replaced by elementary chlorine or bromine; the other can be replaced



Scheme 14

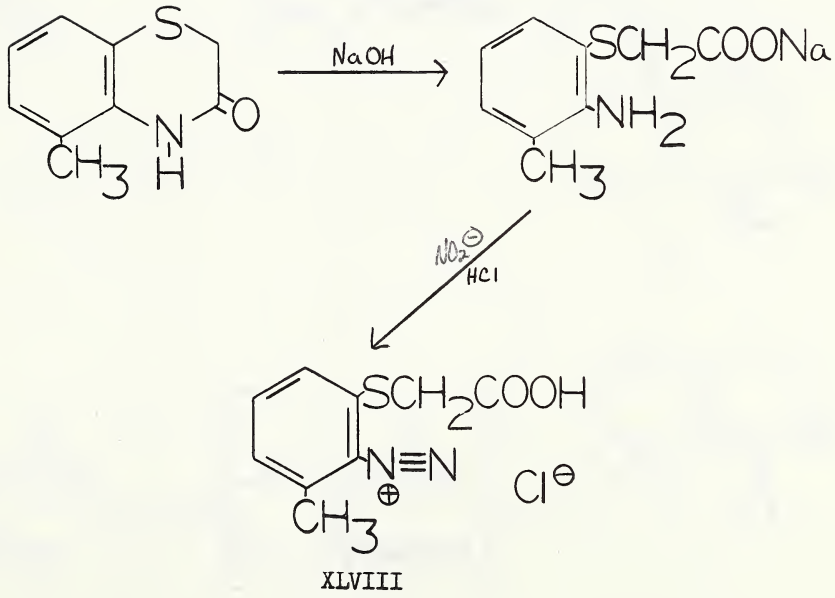
under forcing conditions. The dihalo derivative (XLV) is converted to a ketone (XLVI) using concentrated sulfuric acid (39). This ketone can then be hydrolyzed by the action of base (Scheme 15). Monochloro derivatives react easily with alcohols to give ethers, and will react with aromatic amines, phenols and thiophenols (39,25).

The lactam ring of 3,4-dihydro-3-oxo-2H-1,4-benzothiazines will open in base, yielding (o-aminophenylthio)acetic acids. Subsequent acidification recloses the ring. If sodium nitrite is added to an alkaline solution of (1-amino-2-methylphenylthio)acetic acid and the solution dropped into hydrochloric acid, diazotization will occur before ring closure (40) (Scheme 16).



XLV XLVI XLVII

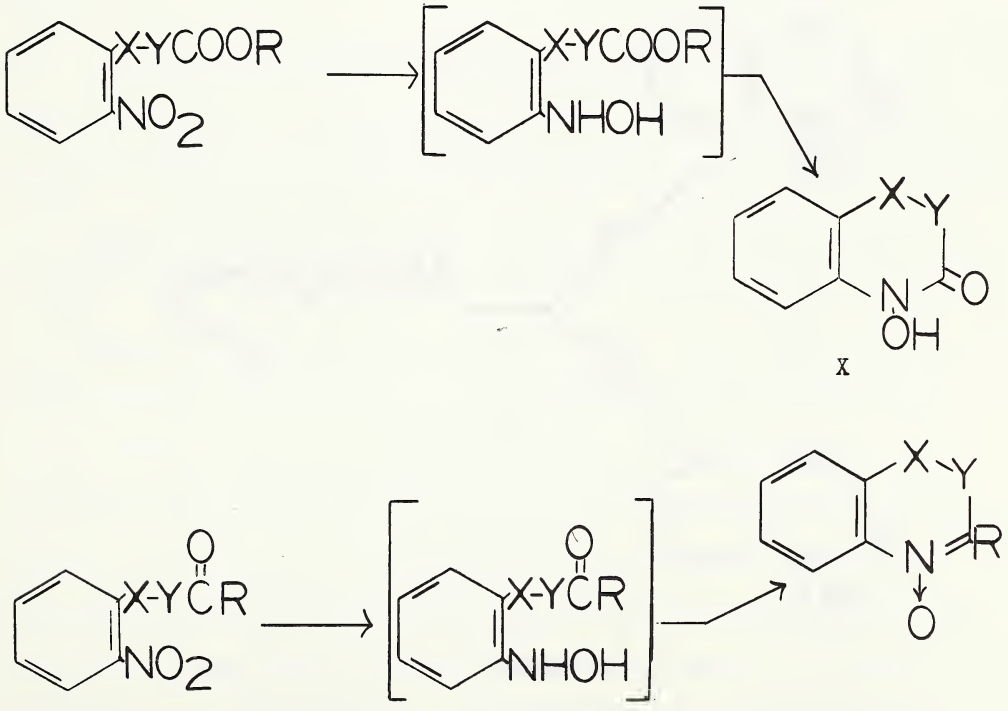
Scheme 15



XLVIII

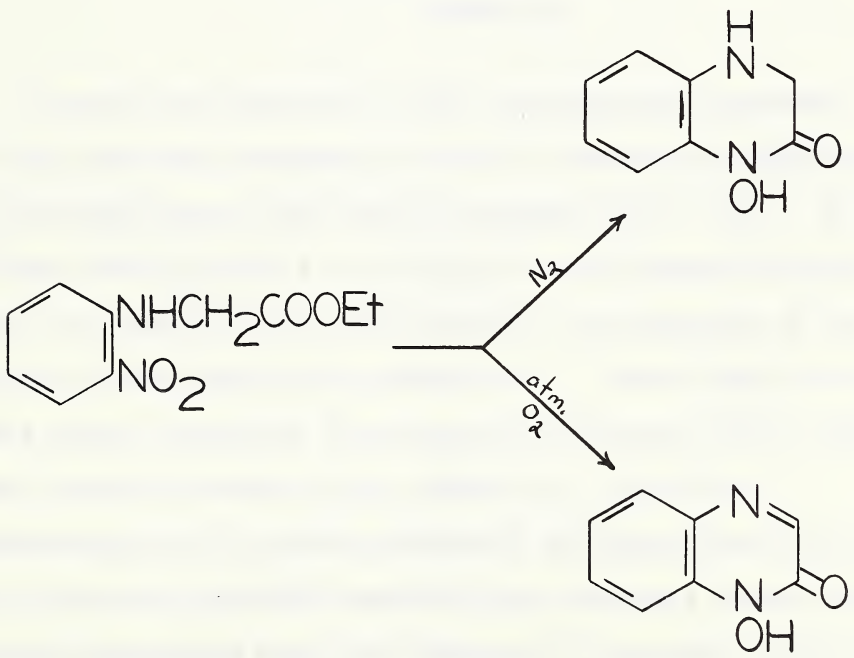
Scheme 16

Cyclic hydroxamic acids have been synthesized by a variety of methods (1). A method of general application which permitted the synthesis of various types of cyclic systems was introduced in 1961. Coutts, Wibberley and co-workers investigated the use of palladium-charcoal catalyst in conjunction with hydrazine hydrate, cyclohexane or sodium borohydride (9, 41, 42) as reducing systems and found that they were capable of reducing aromatic nitro groups to hydroxylamines. If the resulting hydroxylamino group was suitably oriented with respect to an acid, ester or ketone group, spontaneous cyclization occurred, and yielded either an N-hydroxy compound or an N-oxide (Scheme 17).



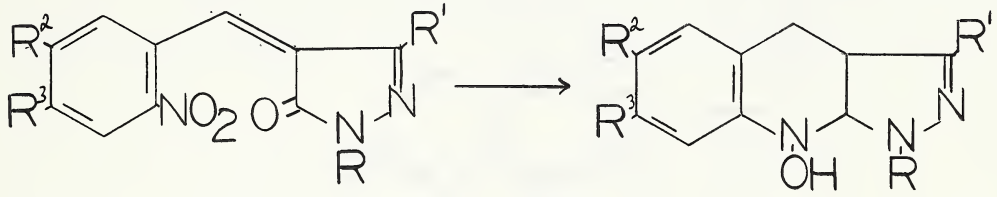
Scheme 17

The combination of palladium-charcoal and sodium borohydride has proven to be a most effective reducing system. It has been used in the synthesis of hydroxamic acid derivatives of many cyclic systems, including quinoxalines, quinolines, pyrazoloquinolines, benzothiazines, benzoxazines, and triazanaphthalines (1, 5, 9, 11, 14, 41-47). Quinoxalines, for example, (X; X-Y = $NHCH_2$) were prepared by reducing ethyl N-o-nitrophenylglycine to give 1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinoxaline. If this reduction was carried out in the absence of nitrogen, however, the reduction yielded the 1,2-dihydroquinoxaline (X; X-Y = N=CH) (Scheme 18).



Scheme 18

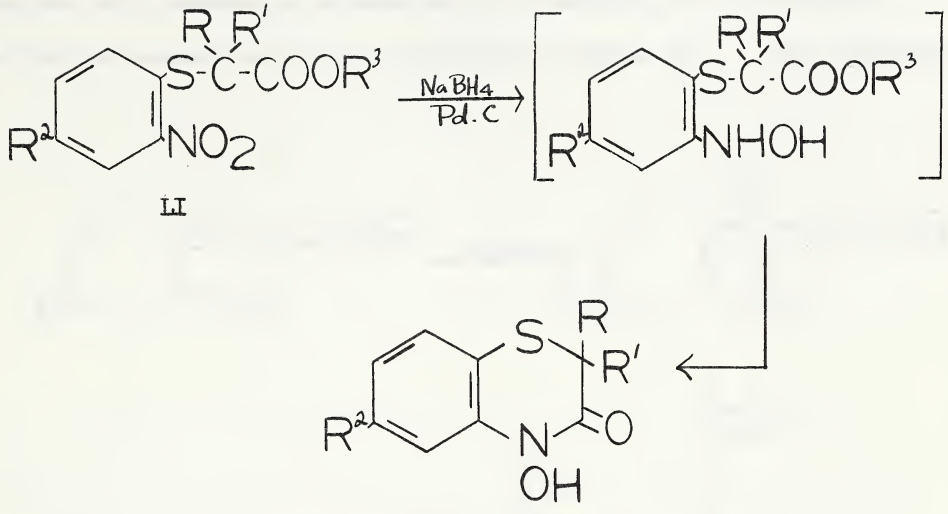
Similarly, reduction of ethyl β-(o-nitrophenyl)propionate yielded the tetrahydroquinoline (X; X-Y = CH_2CH_2) and pyrazoloquinolines (XLIX) were prepared by reducing a suitably substituted pyrazolone (L) (44) (Scheme 19).



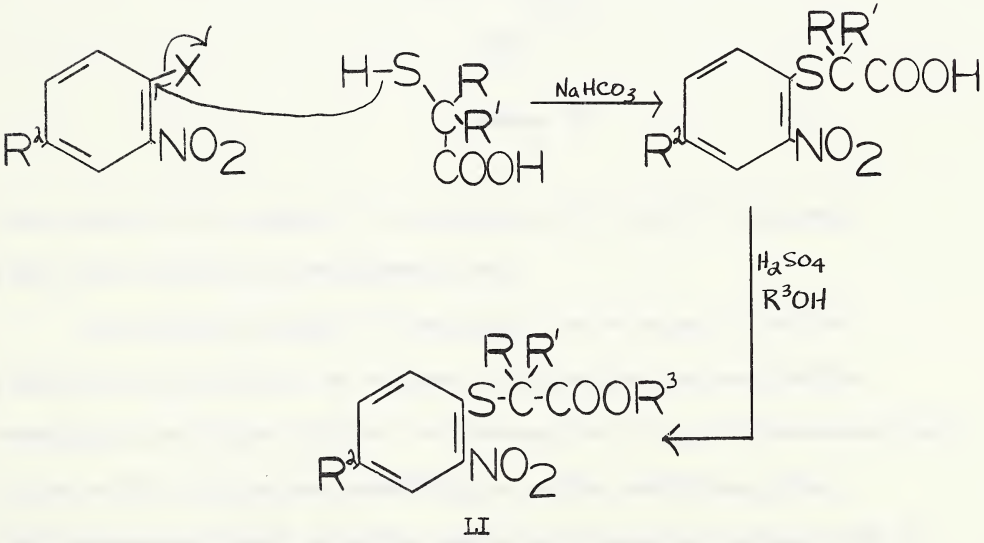
XLIX

Scheme 19

A great many derivatives of 2H-1,4-benzothiazine hydroxamic acids have also been synthesized by means of reductive cyclizations using palladium-charcoal and sodium borohydride (43, 45, 46). It was found that the products of the reduction were dependent upon the solvent, the length of time of the reaction, the temperature of the reaction, and the nature of the substituents. Coutts, Smith and co-workers reduced substituted (o-nitrophenylthio)acetates (LI) in this way and obtained hydroxamic acids (Scheme 20). Reaction of α-mercaptoacids with o-chloronitrobenzenes and esterification of the acid so produced yielded the necessary ester precursors (Scheme 21). The same investigators showed that reduction of the acids (LI; R^3 = H) also produced hydroxamic acids (45). The corresponding sulfones (LII) were prepared by oxidizing the substituted (o-nitrophenylthio)-

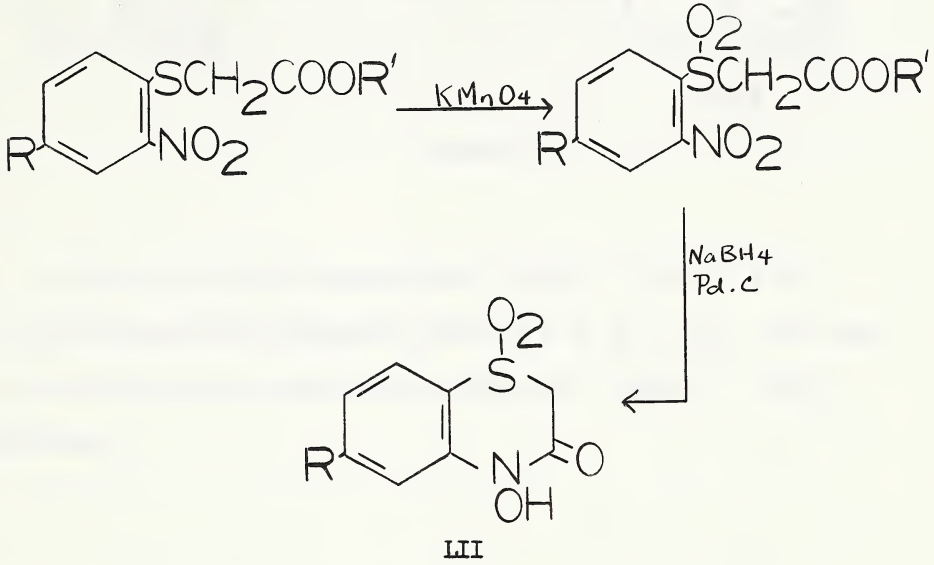


Scheme 20



Scheme 21

acetates with potassium permanganate and reducing the products with palladium-charcoal and sodium borohydride (Scheme 22). This synthetic

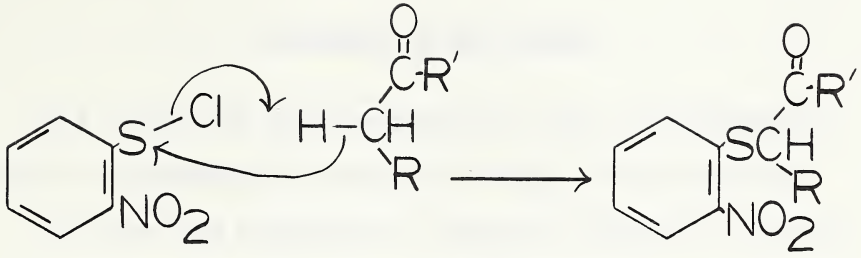


LII

Scheme 22

route proved to be superior to oxidizing the sulfide hydroxamic acids with potassium permanganate (46).

An alternate method of producing the necessary (o-nitrophenylthio)-derivatives to be used in palladium-charcoal/sodium borohydride reduction studies is condensation of o-nitrobenzenesulfenyl chloride with substances containing an active methylene group. o-Nitrobenzenesulfenyl chloride reacts with numerous ketones (48) to give α-(o-nitrophenylthio)ketones (LIII) in good yields (Scheme 23). It condenses with acetophenone, acetone and ethyl acetoacetate to



LIII

Scheme 23

give ω-(o-nitrophenylthio)acetophenone (LIIIa; R = H, R^1 = Ph), α-(o-nitrophenylthio)propanone (LIIIb; R = H, R' = CH_3), and ethyl α-(o-nitrophenylthio)acetoacetate (LIIIc; R = COOEt, R' = CH_3), respectively.

STATEMENT OF THE PROBLEM

This project was approached with the idea of investigating further the preparation and properties of 2H-1,4-benzothiazines.

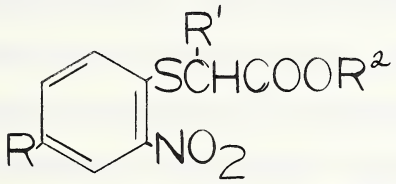
The author was interested in reductive cyclization of appropriate α-(o-nitrophenylthio)-esters and -ketones, especially the latter, in the hope that 2H-1,4-benzothiazine N-oxides or N-hydroxy compounds would be formed.

Also of interest was an investigation of new methods of characterizing 2H-1,4-benzothiazine hydroxamic acids.

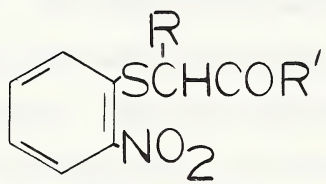
In addition, it was felt that a knowledge of the products obtained by the action of hydrochloric acid and sodium hydroxide on 2H-1,4-benzothiazine hydroxamic acids would be of assistance in identifying the products of the metabolism of benzothiazines in rats.

DISCUSSION

Acids and esters of general formula LI and ketones possessing structure LIII were the required precursors for the proposed reductive cyclization studies. The acids, LIa-LIf, were readily obtained by the nucleophilic attack of various ∝-mercaptoacids on suitably substituted o-chloro- or o-bromonitrobenzenes as illustrated earlier in Scheme 21. The acids were isolated in good yield, generally greater



LI



LIII

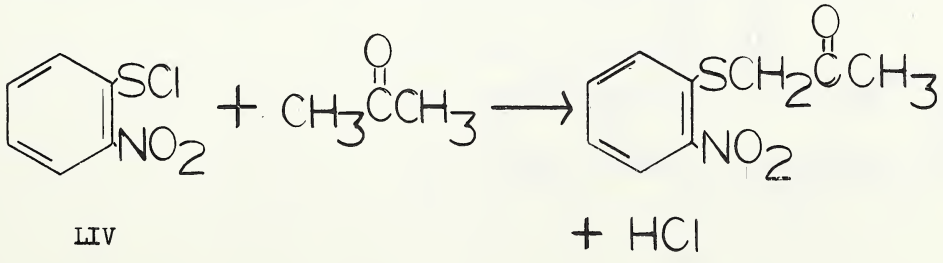
	R	R^1	R^2
a)	H	CH_2COOH	H
b)	Br	CH_2COOH	H
c)	CH_3	CH_2COOH	H
d)	CF_3	CH_2COOH	H
e)	Cl	CH_2COOH	H
f)	H	H	H
g)	H	CH_2COOCH_3	CH_3
h)	Br	CH_2COOCH_3	CH_3
i)	CH_3	CH_2COOCH_3	CH_3
j)	CF_3	CH_2COOCH_3	CH_3
k)	Cl	CH_2COOCH_3	CH_3
m)	H	H	CH_3

	R	R^1
a)	H	CH_3
b)	H	Ph
c)	COOEt	CH_3
d)	COOEt	Ph
e)	$COCH_3$	CH_3
f)	CONHPh	CH_3
g)	CN	NH_2

than 60 per cent of the theoretical. They were characterized by means of infrared studies, which confirmed that each product contained nitro and carboxylic acid groups, and by comparison of their melting points with those reported in the literature. Analytical data was also obtained for the characterization of (4-chloro-o-nitrophenylthio)-succinic acid (LIe).

Each ester (LIg-LIm) was prepared by a Fischer-Speier (49) esterification of the corresponding acid. The esters were readily obtained in excellent yields, and in most cases were not purified before proceeding with reductive cyclization. They were identified by means of their infrared spectra, their melting points, if solids, and in the case of the 4-chloro derivative, by elemental analysis. One ester (LIi) previously reported as an oil (43), was resolved to crystalline form by trituration with ethanol and was characterized by infrared studies and by elemental analysis.

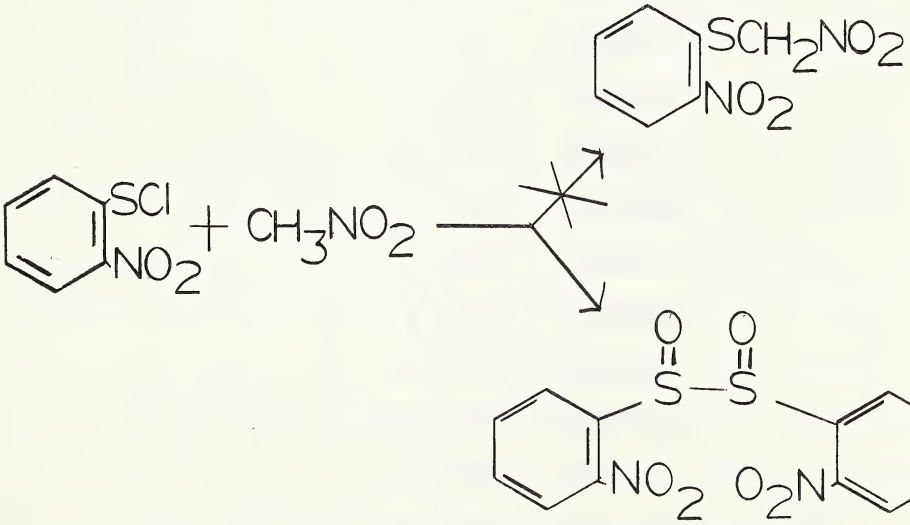
The ketones LIIIa-LIIIg were prepared by interaction of o-nitrobenzenesulfenyl chloride (LIV) with compounds possessing an active methylene group. A typical example of this reaction, the preparation of 1-(o-nitrophenylthio)propan-2-one (LIIIa) is given below (Scheme 24).



Scheme 24

The reaction was carried out by heating the reactants in acetonitrile for various periods of time. Acetonitrile has been recommended (48) as the most suitable solvent for this reaction. Yields of products were very good, all being above 80 per cent of the theoretical. Products were characterized by comparison of melting points with those reported, as well as by means of infrared studies and analytical data. Functional group absorption bands due to the nitro group and the ketone function were observed in each spectrum.

An attempted reaction which was unsuccessful was the condensation of nitromethane and o-nitrobenzenesulfenyl chloride using the same conditions as above. Bis(o-nitrophenyl)disulfoxide (LV) was the only product isolated from the reaction mixture (Scheme 25). It was

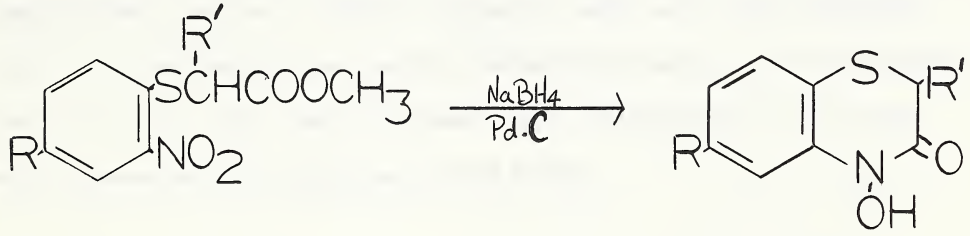


LV

Scheme 25

characterized by means of its infrared spectrum, an elemental analysis, and a comparison of its melting point with that reported.

Esters LIg-LIm were reduced by means of sodium borohydride in the presence of palladium-charcoal (Scheme 26). In these reductive cyclization studies, it was noted that the yield of product depended on

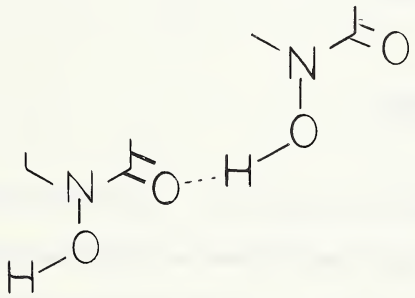


LVI

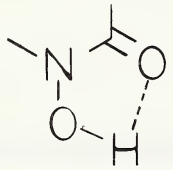
Scheme 26

	R	R^1	
a)	H	CH_2COOCH_3	
b)	H	CH_2COOH	
c)	CH_3	CH_2COOCH_3	
d)	CH_3	CH_2COOH	
e)	Br	CH_2COOCH_3	
f)	Br	CH_2COOH	
g)	CF_3	CH_2COOCH_3	
h)	CF_3	CH_2COOH	
i)	Cl	CH_2COOCH_3	
j)	H	H	
k)	H	H	SO_2 replaces S.

the length of time over which the ester was added to the reducing system, as well as on the solvent used, as had been reported previously (45). Yields in this series of reductions were variable, but in most cases were not very high. The products were characterized by means of their melting points, infrared spectra, and analytical data where necessary. The infrared spectra of cyclic hydroxamic acids are quite diagnostic (50). In particular, two carbonyl absorption bands are often observed, due to the fact that these compounds exist as mixtures of the inter- and intra-molecularly hydrogen-bonded forms.



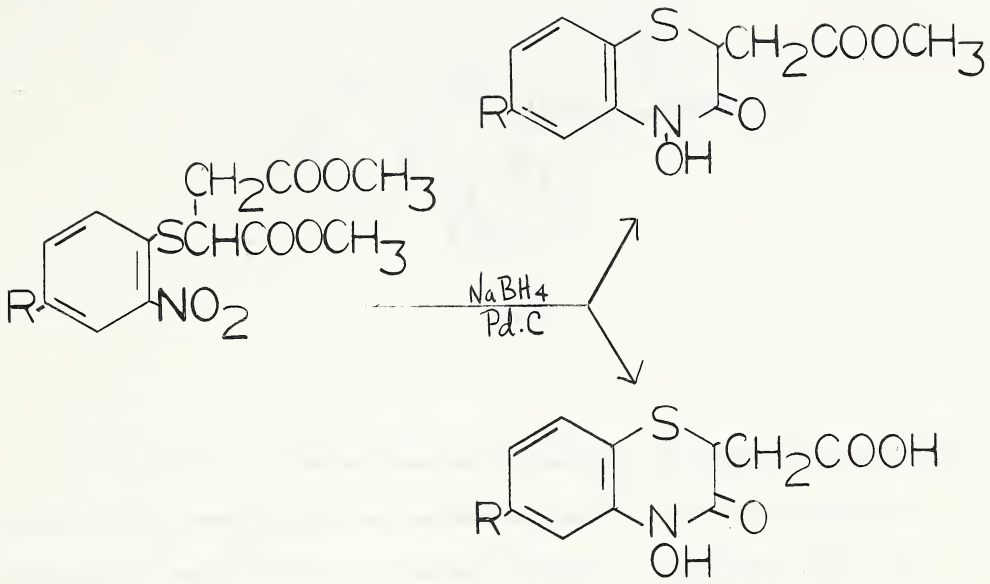
Intermolecular Bonding



Intramolecular Bonding

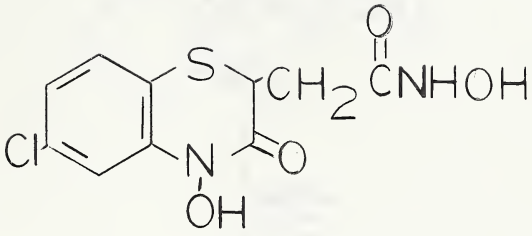
The ease with which the ester group of the hydroxamic acids of general formula LVIa-LVIi can be hydrolyzed was exhibited in this series of reductions. Even in the slightly basic reducing medium, the ester group of three of these hydroxamic acids (LVIa, LVIc, and LVIg) was hydrolyzed to the acid during reduction (Scheme 27). No ester product was isolated from these reactions.

It was felt that a molecule containing both a cyclic and an acyclic hydroxamic acid grouping might show some interesting pharma-



Scheme 27

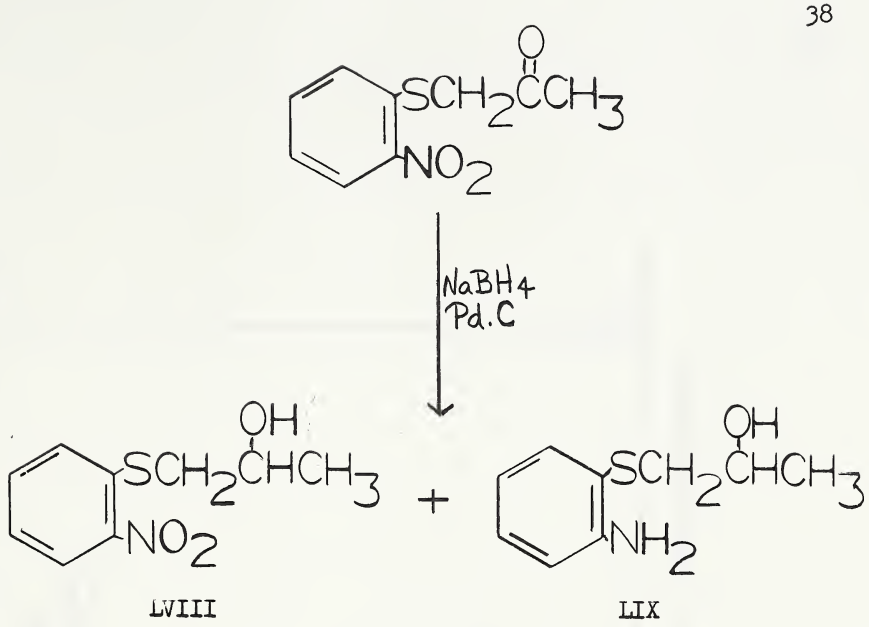
cological activity. With this in view, (6-chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl) acetohydroxamic acid (LVII) was prepared by interacting methyl (6-chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIi) and hydroxylamine hydrochloride in potassium hydroxide solution. The product analyzed satisfactorily for $C_{10}H_9ClN_2O_4S$ and yielded a deep violet color with ethanolic ferric chloride solution. Infrared data also supported structure LVII, absorption bands ascribable to carbonyl, hydroxyl, and secondary amine groups being present in the spectrum. This compound was subjected to antibacterial testing, however it showed no activity against Escherichia coli and Staphylococcus aureus at a concentration of 40mg. per cent.



LVII

Reduction of the ketones and ketoesters of general formula LIII using sodium borohydride and palladium-charcoal did not proceed as smoothly as reduction of the esters LIg-LIm. Previously (51), it was thought that these would cyclize using this reduction system to the N-oxide product. Peel, however, was unable to isolate any N-oxide products when he reduced ketoesters with the sodium borohydride/palladium-charcoal reduction system, and he hypothesized that the palladium catalyst was in some way being "poisoned" during the reduction. The present study, therefore, was undertaken in an attempt to clarify what reactions were taking place when β-ketoesters were reduced by means of sodium borohydride and palladium-charcoal.

Reduction of (o-nitrophenylthio)propan-2-one (LIIa) with sodium borohydride in the presence of palladium-charcoal (Scheme 28) yielded 1-(o-nitrophenylthio)propan-2-ol (LVIII), which was characterized by means of its 3,5-dinitrobenzoate. This nitro-alcohol was also the product of the reduction of LIXa using sodium borohydride without catalyst. An additional product of the catalyzed reaction was 1-



LVIII LIX

Scheme 28

(o-aminophenylthio)propan-2-ol (LIX), which was isolated in small yield. Its formation indicated that the catalyst still had some activity. The assignment of structure LIX to the product just described was made for the following reasons. Its infrared spectrum was identical with that of a sample of the same compound prepared by reacting propylene glycol with o-aminothiophenol in absolute ethanol and metallic sodium (52). The mass spectrum of the product showed a molecular ion at m/e 183 which was also the base peak. A molecular formula of $C_9H_{13}NOS$ satisfies this molecular weight. In addition, strong fragment ions of mass 139, 125 and 124 were present in the spectrum (Figure 1). Rationalization of these fragment ions is shown in more detail for the related phenyl derivative (Scheme 35).

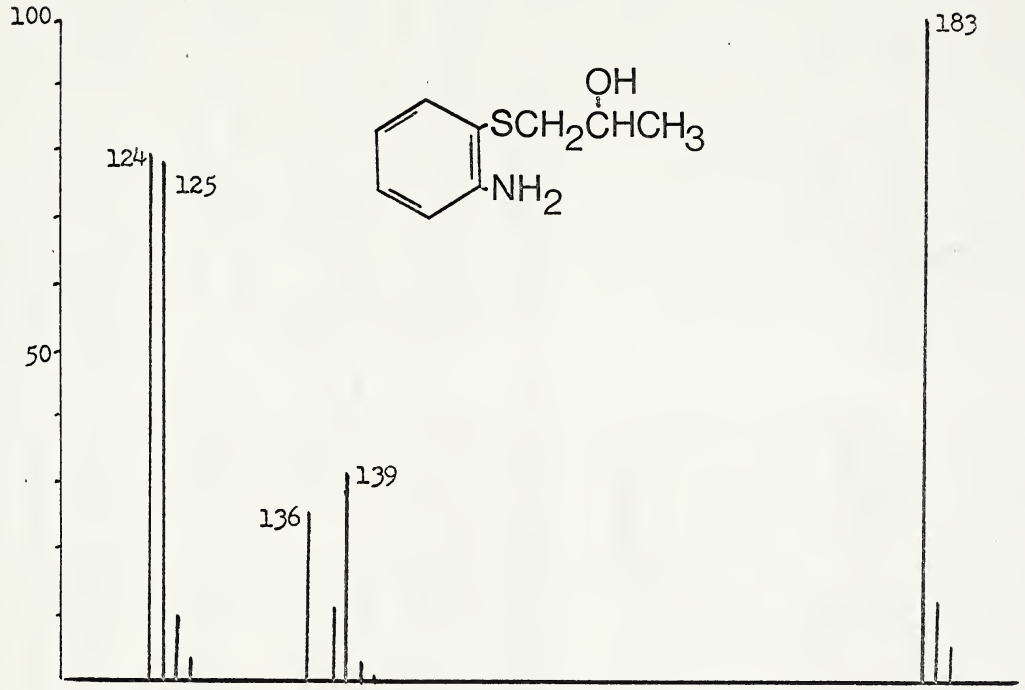
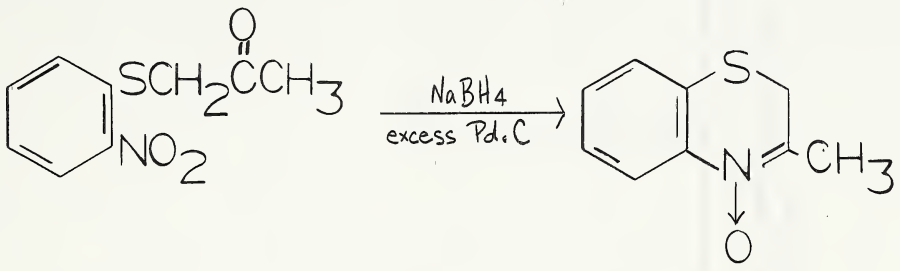


Figure 1: A portion of the mass spectrum of 1-(o-aminophenylthio)-propan-2-ol (LIX).

It was felt that by increasing the quantity of the palladium-charcoal catalyst, the apparent "poisoning" might be overcome, and the desired N-oxide product (LX) might be obtained (Scheme 29).



LX

Scheme 29

The neutral fraction from the reduction of (o-nitrophenylthio)propan-2-one by means of sodium borohydride and five times the usual amount of palladium-charcoal was a complex mixture which was not identified. There were no peaks in the infrared spectrum ascribable to a nitro group or a carbonyl function, indicating that both these functions had been reduced during the reduction. The basic fraction from this reduction was a mixture which was not separated. The mass spectrum of the mixture was helpful (Figure 2). From it, it was possible to deduce tentatively that the components of the mixture were:

a) 7-chloro-3,4-dihydro-3-methyl-2H-1,4-benzothiazine (LXI)

b) 1-(o-aminophenylthio)propan-2-ol (LIX) and

c) 3,4-dihydro-3-methyl-2H-1,4-benzothiazine (LXII).

The formation of LIX is most readily explained (Scheme 30).

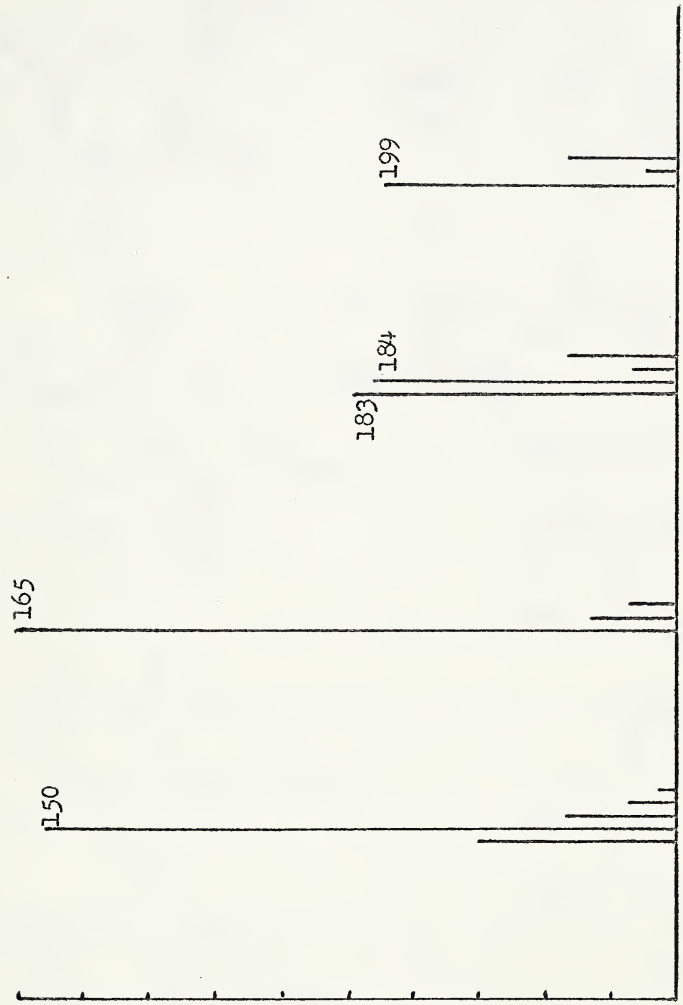
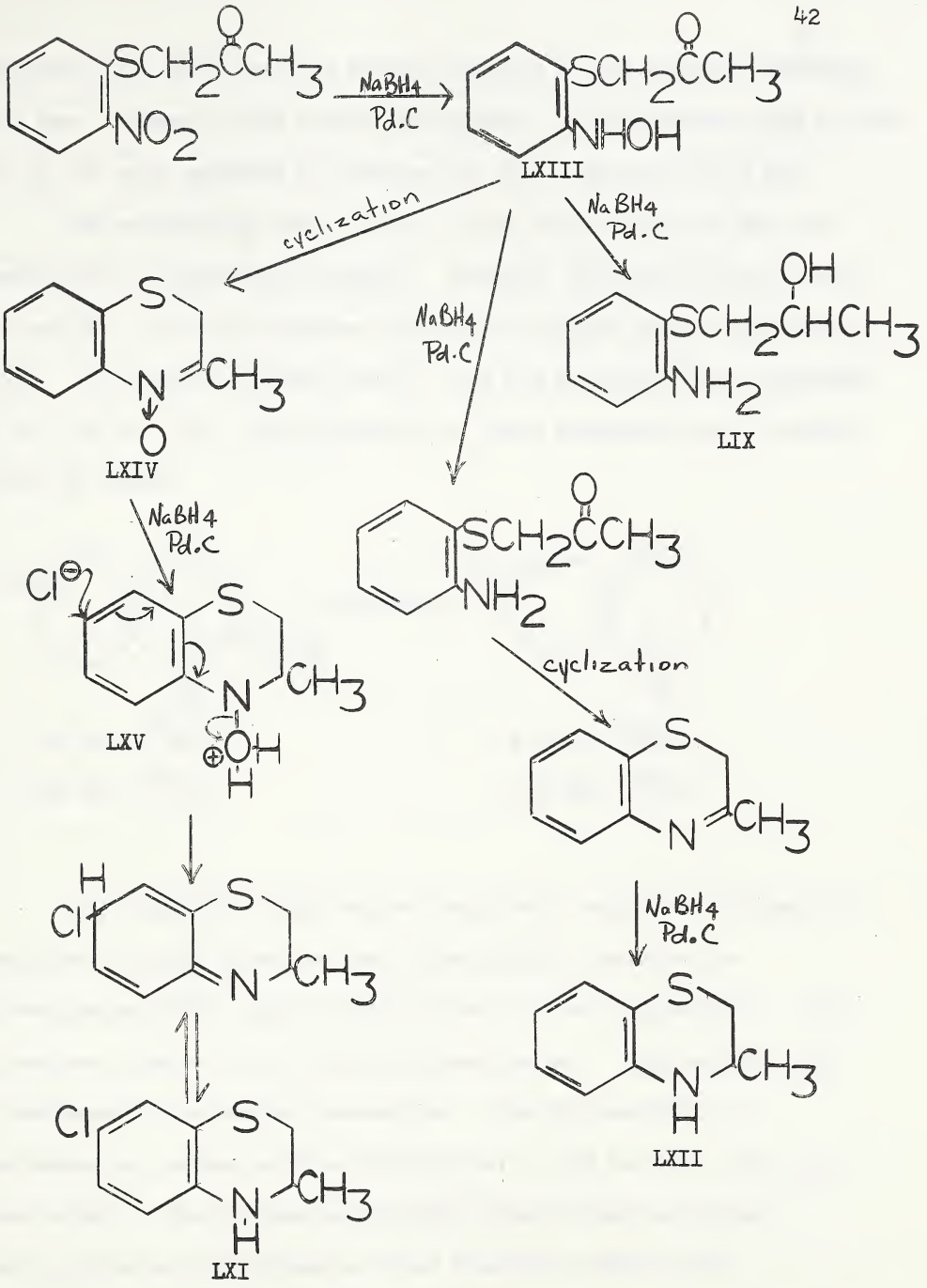


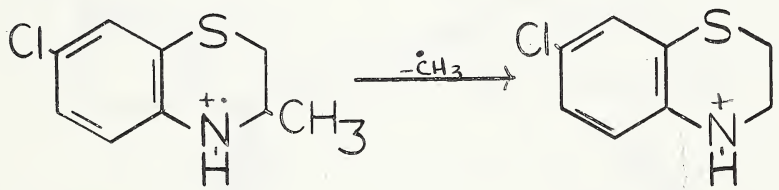
Figure 2: A portion of the mass spectrum of the basic fraction of the reduction of 1-(o-nitrophenylthio)propan-2-one.


NaBH4
Pd.C
LXIII
cyclization
LXIV
LIX
LXV
cyclization
LXII
LXI

Scheme 30

Both the nitro group and the ketone function of the starting material have been reduced by the sodium borohydride. The abundant peak at m/e 183 in the mass spectrum is ascribed to the molecular ion of LIX.

The possibility that LXI was one of the products of the reduction was at first sight remote. However, molecular ions of mass 199 and 201 and their relative intensities support such a conclusion (53). In addition, strong $(m-15)^+$ ions are observed in the spectrum at m/e 184 and 186. The formation of these fragment ions is rationalized as shown:

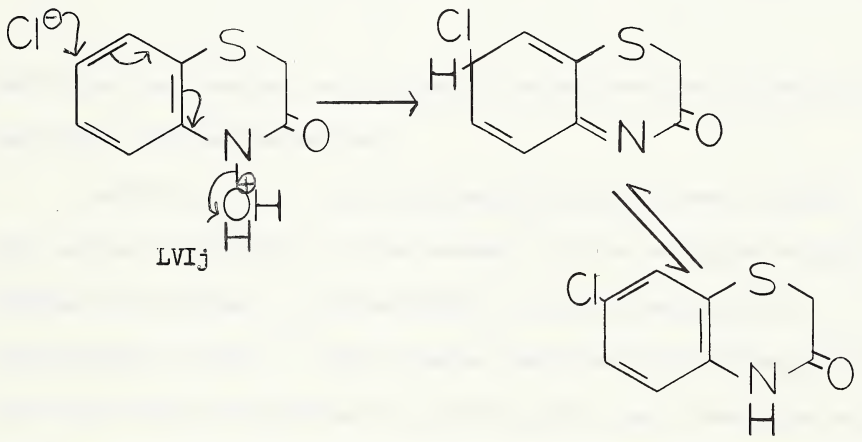


m/e 199 (^{35}Cl)
m/e 201 (^{37}Cl)

m/e 184 (^{35}Cl)
m/e 186 (^{37}Cl)

The formation of LXI can be tentatively explained (Scheme 30). Reduction of LIIIa gives as one of the initial products the hydroxylamine LXIII, which then cyclizes to the N-oxide LXIV. This is reduced further to the cyclic hydroxylamine. Hydrochloric acid is employed in the work-up procedure. The OH group will be protonated and attack of the chloride ion on LXV as shown would give rise to LXI. The protonated hydroxyl group of LXV is a good leaving group and its presence would therefore permit such a nucleophilic attack by the Cl^- ion. Although speculative, there are

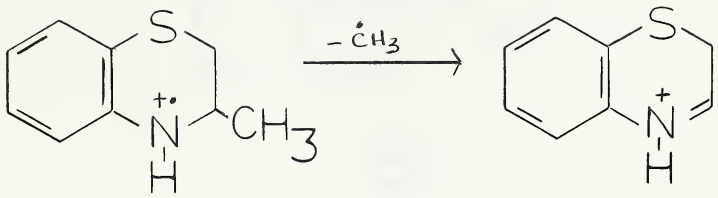
ample literature references in support of the formation of LXI in this manner. When reduced by means of sodium borohydride and palladium-charcoal, many aromatic nitro compounds which possess an ester or a ketone group in a position suitably oriented with respect to the o-nitrophenyl group are converted into cyclic N-oxy or N-hydroxy compounds (1). In addition, hydrochloric acid is known (54) to react with a cyclic hydroxamic acid (LVIj) related in structure to LXV, in the manner shown (Scheme 31).



Scheme 31

A possible mechanism for the formation of LXII by reduction of the nitro-ketone LIIIa is also given in Scheme 30. The base peak in the mass spectrum of the basic fraction from the reduction of LIIIa is of m/e 165. The most abundant fragment ion is of mass 150. The ions proposed below are compatible with this observation (Scheme 32).

Obviously, further work must be done to substantiate these observations. Nevertheless, this study at least suggests that



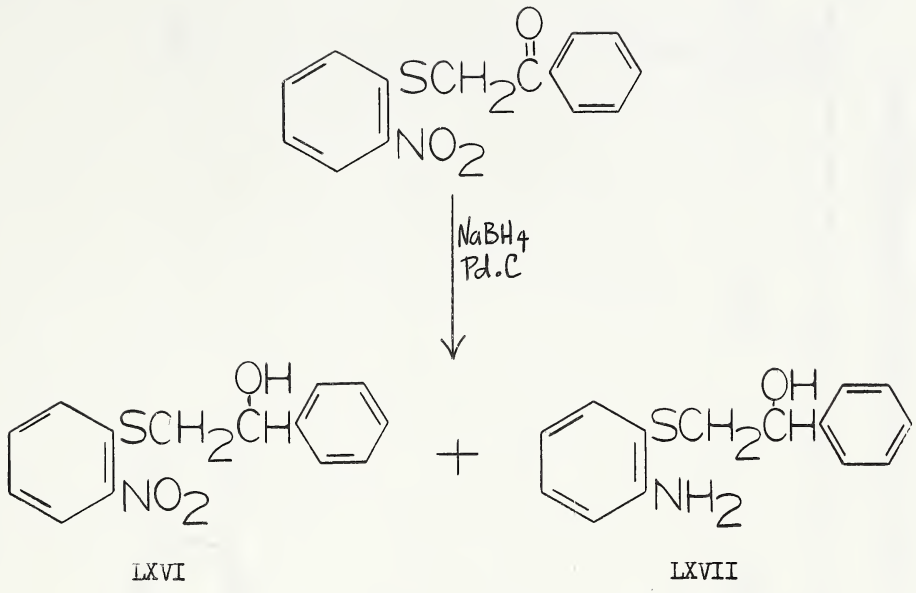
LXII; m/e 165 m/e 150

Scheme 32

benzothiazine N-oxides and N-hydroxy derivatives can be prepared by reductive cyclization methods.

Reduction of ω-(o-nitrophenylthio)acetophenone (LIIIb) with sodium borohydride in the presence of the palladium catalyst (Scheme 33) yielded a nitro-alchohol, 2-(nitrophenylthio)-1-phenylethanol (LXVI). The infrared spectrum of this compound showed absorption bands ascribable to a nitro group, and showed the absence of a carbonyl function in the molecule. Its melting point was very close to that reported and it was further characterized by the preparation of its ρ-nitrobenzoate derivative. 2-(o-Aminophenylthio)-1-phenylethanol (LXVII) was also obtained from the reduction in very small yield. Its infrared spectrum was identical with that of the base isolated when ω-(o-nitrophenylthio)acetophenone was reduced using sodium borohydride and five times the usual amount of palladium catalyst.

The neutral fraction of the reduction of LIIIb using sodium



LXVI LXVII

Scheme 33

borohydride and excess palladium-charcoal was a mixture. One component of this mixture was isolated using column chromatography. The remaining components could not be separated and were not identified. The mass spectrum of the isolated fraction showed a molecular ion of mass 448 (Figure 3). A molecular formula of $C_{28}H_{20}N_2S_2$ satisfies this. Also present in the mass spectrum was a strong $(m-2)^+$ ion at m/e 446. The most abundant fragment was of mass 224. The ions proposed in Scheme 34 are compatible with these observations. This fraction, therefore, is identified as bis[2-(3-phenyl-2H-1,4-benzothiazine)] (LXVIII). The compound analyzed satisfactorily for $C_{28}H_{20}N_2S_2$. Its melting point is higher than that reported by Fujii (55), who isolated this compound when attempting to prepare the picrate of 3-phenyl-4H-1,

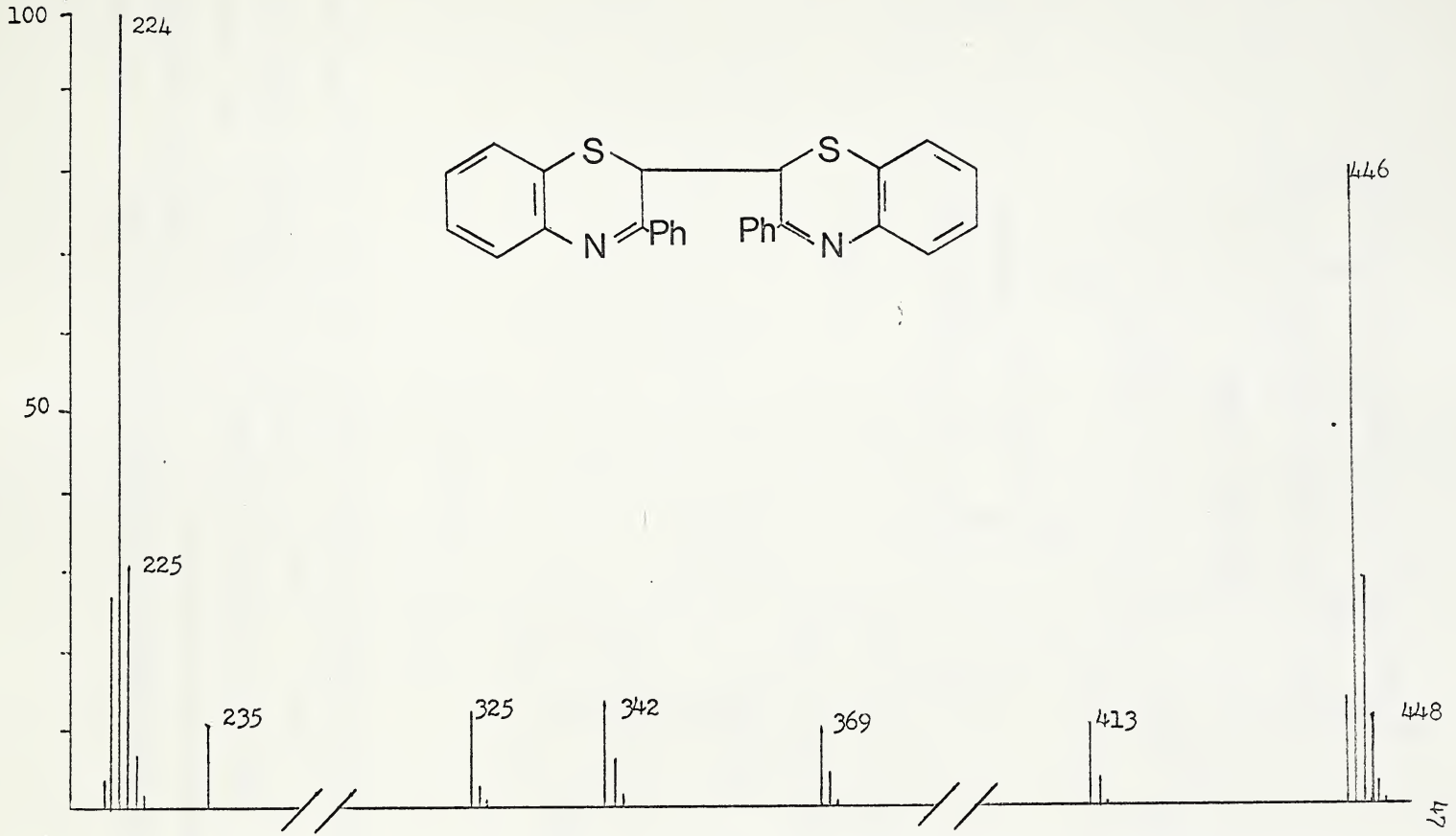
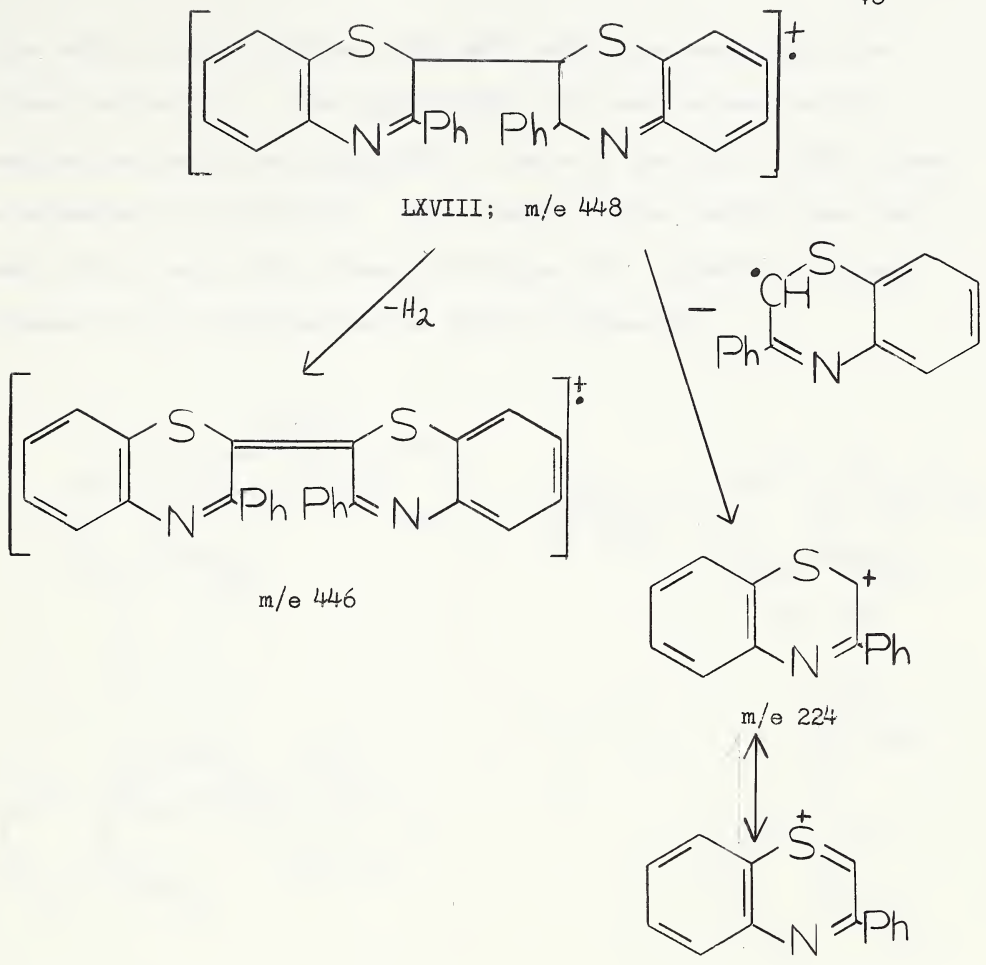


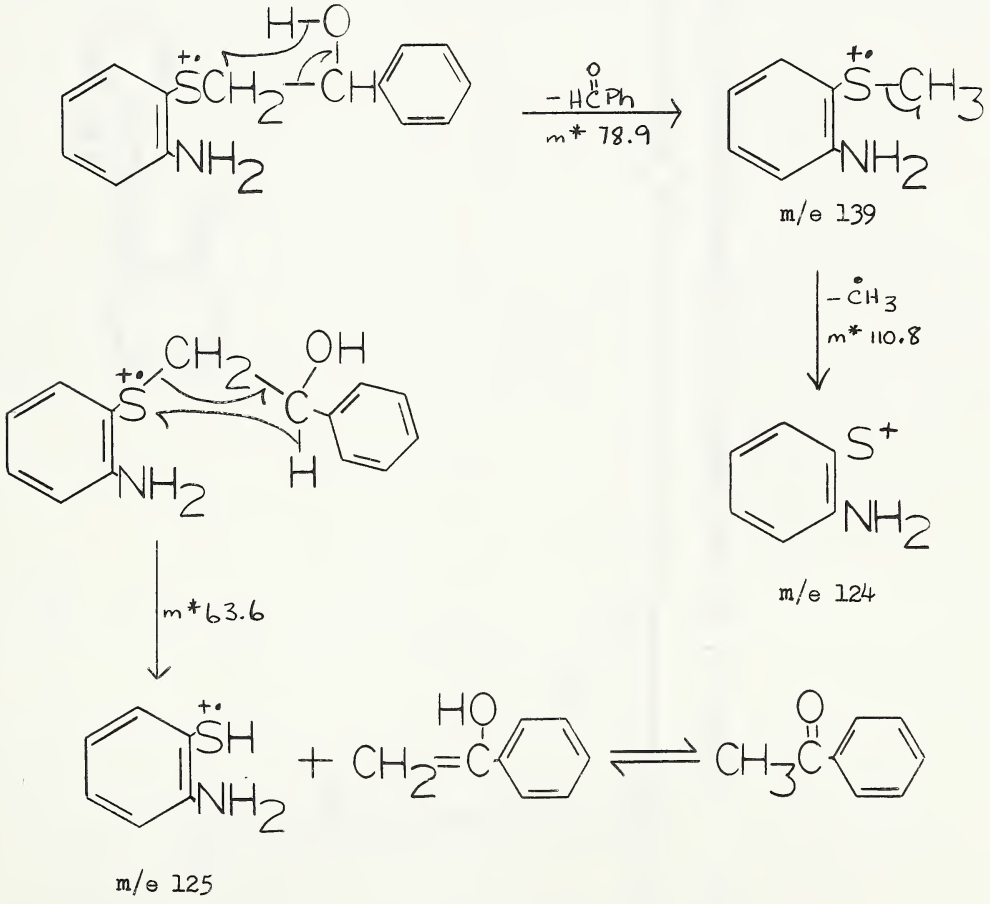
Figure 3: A portion of the mass spectrum of bis[2-(3-phenyl-2H-1,4-benzothiazine)] (LXVIII)



Scheme 34

4-benzothiazine. The basic fraction of this reduction was identified as 2-(o-aminophenylthio)-1-phenylethanol (LXVII). It gave a red-violet color with two per cent furfural in glacial acetic acid solution, indicative of an amine. The infrared spectrum indicated the absence of nitro and carbonyl functions and showed strong absorp-

tion bands at 3360, 3460 and 1610 cm^{-1}, which are ascribable to a primary amine (56). The hydrochloride salt was prepared and it analyzed correctly for $C_{14}H_{16}ClNOS$. The mass spectrum of LXVII showed a molecular ion at m/e 245. Also present in the spectrum were fragment ions of mass 139, 125 and 124 (Figure 4). Formation of these fragment ions is rationalized as shown in Scheme 35.



Scheme 35

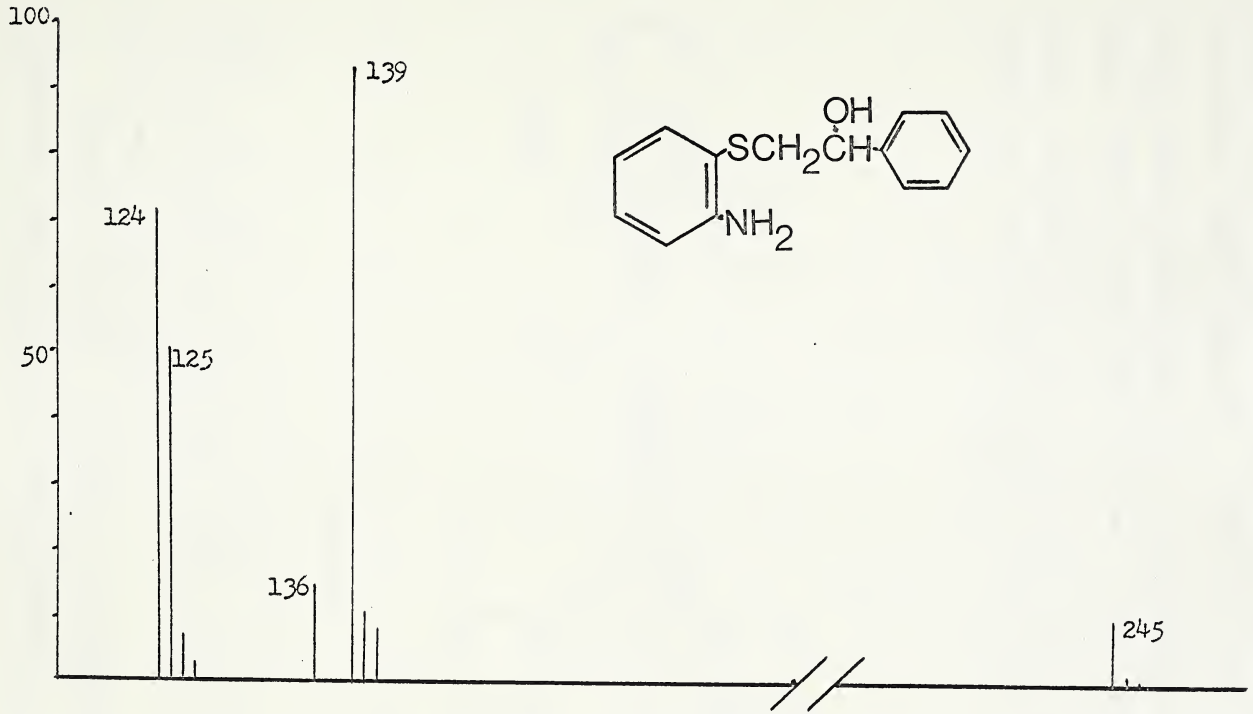
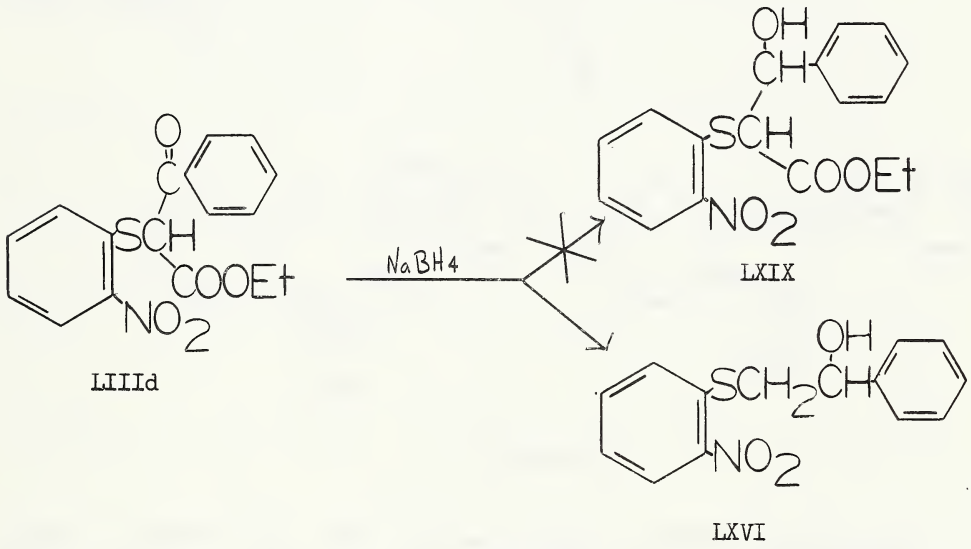


Figure 4: A portion of the mass spectrum of 2-(o-aminophenylthio)-1-phenylethanol (LXVII)

The product of the sodium borohydride reduction of ethyl α-benzoyl- α-(o-nitrophenylthio)acetate (LIIId) was not the expected nitro-alchohol LXIX (Scheme 36). Hydrolysis and decarboxylation occurred during the reduction, and 2-(o-nitrophenylthio)-1-phenyl-ethanol (LXVI) was the product obtained. This compound had been isolated previously from the reduction of ω-(o-nitrophenylthio)-acetophenone. The infrared spectrum of the crude reduction product



LIIId

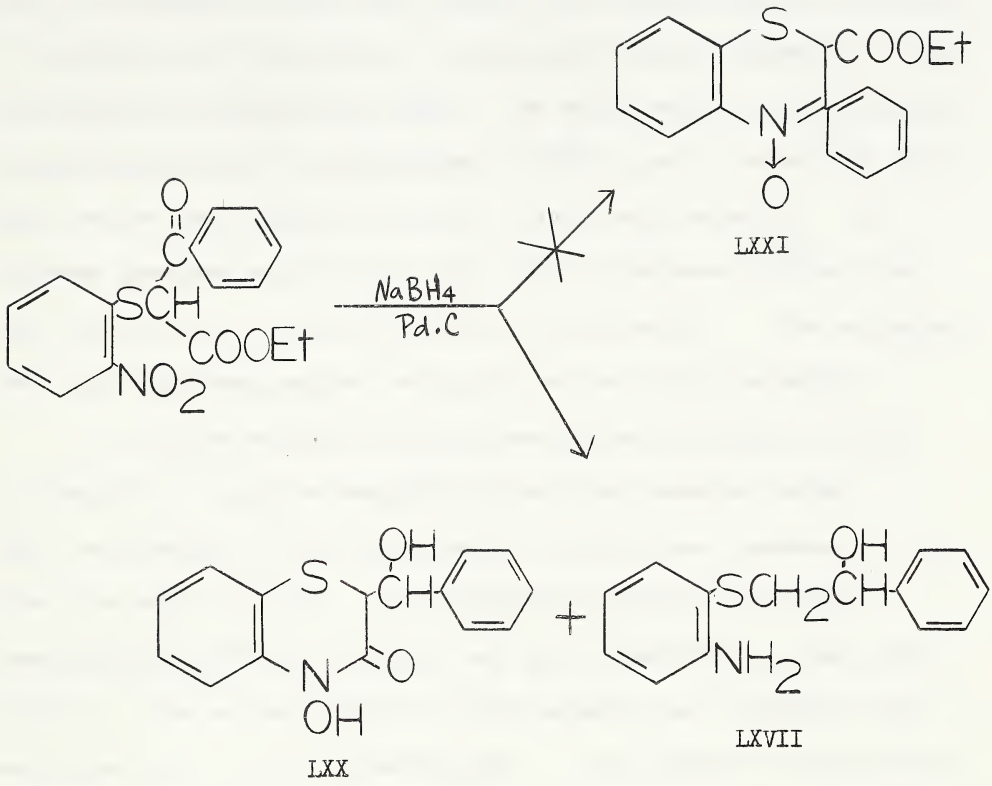
LXIX

LXVI

Scheme 36

showed a weak peak at 1735 cm^{-1} ascribable to an ester function. This would indicate that some ester (LXIX) may have been formed, but it was removed during purification.

Reduction of ethyl α-benzoyl- α-(o-nitrophenylthio)-acetate with sodium borohydride and palladium-charcoal (Scheme 37)



Scheme 37

yielded a neutral oil. This oil was shown by infrared spectroscopy to be a mixture of components which were not separated. The major product of this reduction was the acidic fraction. The violet color obtained upon addition of ethanolic ferric chloride solution and the subsequent characterization of a ferrous chelate showed that the acidic product was the cyclic hydroxamic acid, 1-(3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)benzyl alchohol (LXX). The presence of the hydroxyl group rather than the ketone function in the side chain

of this compound indicated that reduction of the ketone group occurred prior to reduction of the nitro group to the hydroxylamine, thus making it impossible for the ketone to cyclize with the hydroxylamine to yield the desired N-oxide product (LXXI). The basic product of the reaction, 2-(o-aminophenylthio)-1-phenylethanol (LXVII), gave a red-violet color with two per cent furfural in glacial acetic acid solution. Its infrared spectrum was identical with that of the base obtained from the reduction of ω-(o-nitrophenylthio)acetophenone . The carbethoxy group had also been removed during the course of this reduction.

The sodium borohydride/palladium-charcoal reduction of ethyl α-benzoyl-α-(o-nitrophenylthio)acetate was repeated, except that the quantity of palladium-charcoal catalyst was increased to five times the usual quantity. 1-(3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)benzyl alchohol was again identified as the acidic product. The neutral product of this reduction was a mixture which was subjected to column chromatography. One component of the mixture was isolated in this manner. This component was an oil which was not further purified but is tentatively identified as 2-phenylbenzothiazole N-oxide (LXXII). The mass spectrum of LXXII showed a molecular ion of m/e 227, and an $(m-16)^+$ peak at 211, which was also the base peak (Figure 5). An $(m-16)^+$ ion is a fragment characteristic of N-oxides (57) (Scheme 38). Also a strong absorption band at 1260 cm^{-1} in the infrared spectrum ascribable to an N-oxide function (56), substantiates the appropriateness of this structure. The possibility of this compound resulting from the reduction of LIIId is at first sight remote. However,

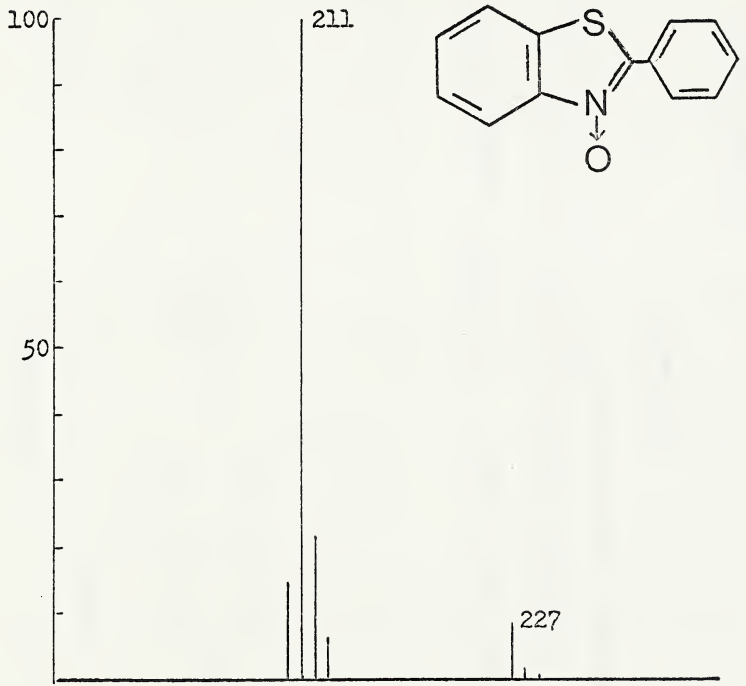
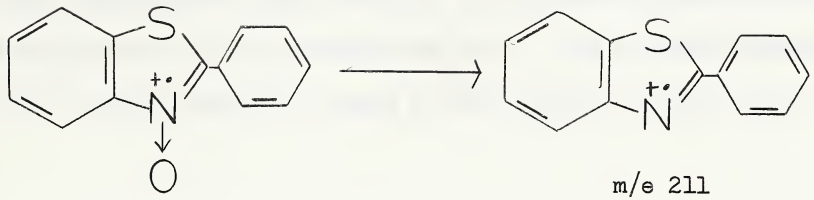


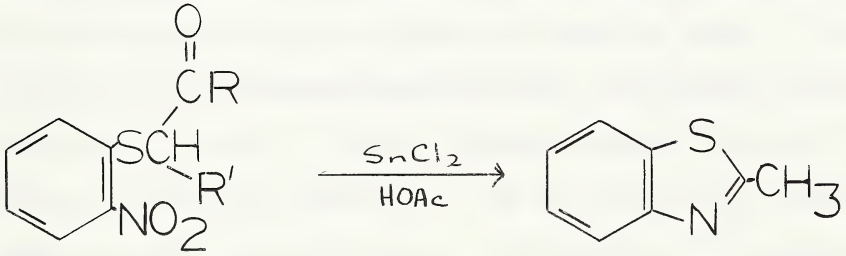
Figure 5: A portion of the mass spectrum of 2-phenylbenzothiazole N-oxide (LXXII).



LXXII; m/e 227 m/e 211

Scheme 38

Finar and Montgomery (58) found that o-nitrophenylthio compounds of type LXXIII, when reduced with stannous chloride, yielded 2-methylbenzothiazole (LXXIV) (Scheme 39). They felt that the reaction

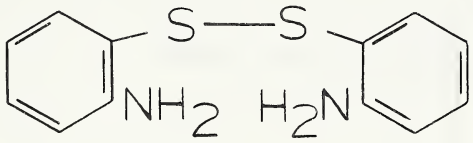


LXXIII LXXIV

Scheme 39

was preceeded by scisson of the S-C bond, followed by condensation of the acetic acid present in the mixture with the thiophenol thus formed. Rupture of the S-C bond also occurs during the reduction of LIIId indicated by the isolation of 2,2'-diaminodiphenyldisulfide in addition

to the N-oxide LXXII. When the reduction mixture was extracted with ten per cent hydrochloric acid solution, 2,2'-diaminodiphenyldisulfide (LXXV) precipitated as its hydrochloride salt. The infrared spectrum of this salt showed absorption bands at 2860, 2595, and 1900 cm^{-1},



LXXV

characteristic of salts of primary amines (59). The free base was generated by basification of a solution of the salt to give shiny yellow plates which melted very close to the reported value. The mass spectrum of 2,2'-diaminodiphenyldisulfide thus produced showed a molecular ion at m/e 248. The most abundant fragment ion in the spectrum was at mass 124 (Figure 6). The ions shown below (Scheme 40) are compatible with this observation. Basification of the acidic extract remaining after removal of the salt of LXXV yielded 2-(o-aminophenylthio)-1-phenylethanol (LXVII) which was identical with the basic product obtained by reducing ω-(o-nitrophenylthio)acetophenone.

Ethyl α-(o-nitrophenylthio)acetoacetate (LIIIc) was also reduced using sodium borohydride and five times the usual amount of palladium-charcoal catalyst. In this reaction, a solid product precipitated from the filtrate remaining after removal of the catalyst.

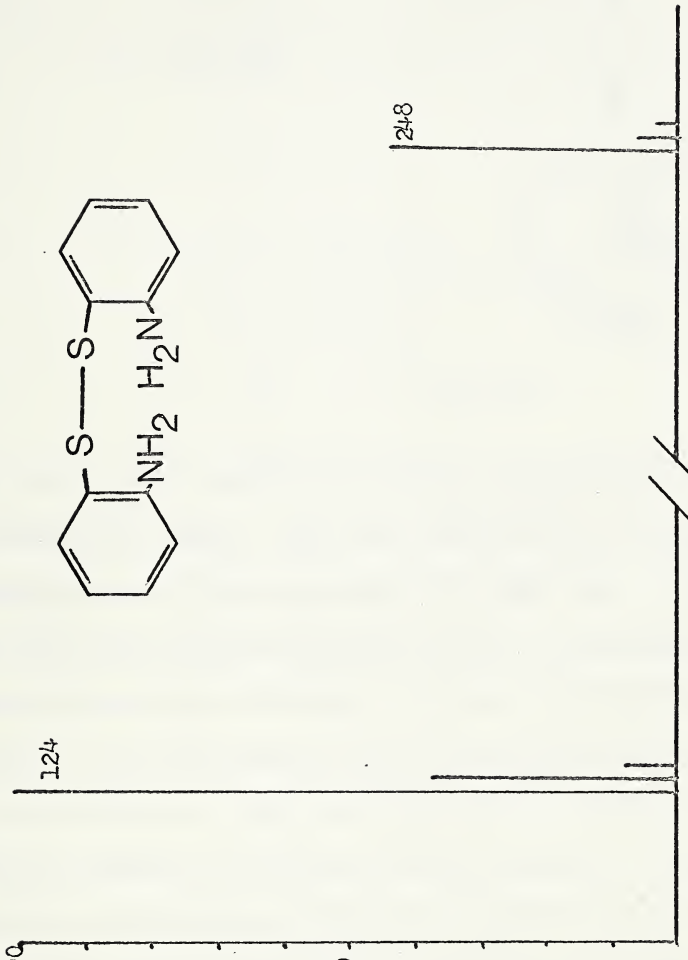
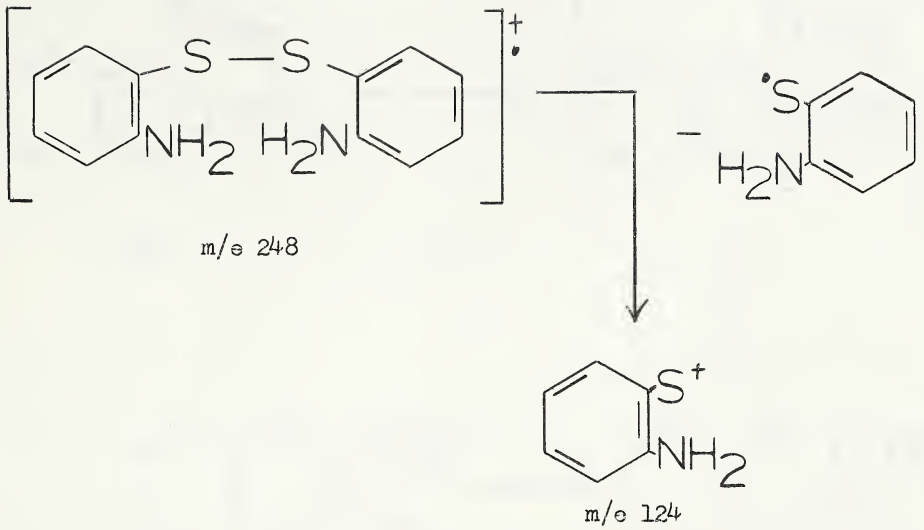
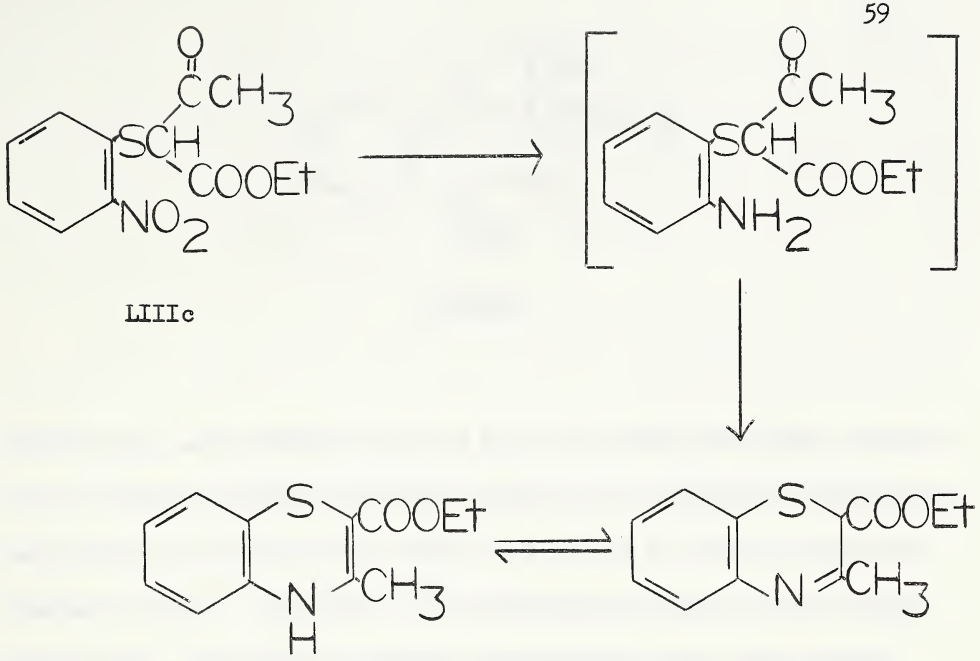


Figure 6: A portion of the mass spectrum of 2,2'-diaminodiphenyl-disulfide (LXXV).



Scheme 40

This solid product proved to be ethyl 3-methyl-4H-1,4-benzothiazine-2-carboxylate (LXXVI), which was characterized by comparison of its melting point with that reported and by NMR data. A 3-proton triplet at τ8.72 and a 2-proton quartet at τ5.83 are ascribed to the ethyl group in the ester side chain. J values for both these signals were 7 cps. A 3-proton singlet at τ7.72 is ascribable to the methyl group in the 3-position. The double bond of the benzothiazine nucleus would be expected to deshield the methyl group. Formation of this product is explained by postulating a reduction of the nitro group to the amine, followed by cyclization with the ketone group(Scheme 41). That it exists in the tautomeric form LXXVI rather than as the 2H-1,4-benzothiazine LXXVII is suggested by the presence of a 1-proton signal at τ4.17 in the NMR spectrum. This peak is in a position as-



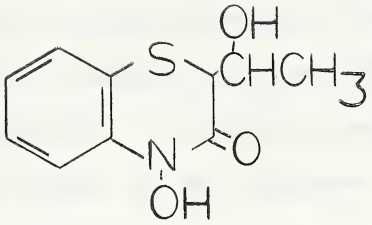
LIIIc

LXXVI LXXVII

Scheme 41

cribable to an NH peak (57), and the proton is readily exchanged in D_2O. Also, the presence of a peak at 1701 cm^{-1} in the infrared spectrum is consistant with an α, β -unsaturated ester structure, and a peak at 3430 cm^{-1} due to an NH function (56), are consistent with the structure. The acid fraction isolated from this reduction formed a violet color in ethanolic ferric chloride solution and was presumed to be 2-(3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)ethanol (LXXVIII). The infrared spectrum of this oil indicated the absence of a nitro function in the molecule. The neutral and basic fractions were complex oils which were not identified.

The cyclic hydroxamic acids were reacted with ten per cent



LXXVIII

hydrochloric acid solution and ten per cent sodium hydroxide solution in an attempt to obtain reference compounds for comparison with possible metabolic products which might be isolated in future biological studies in rats. Treatment of the hydroxamic acids in this manner yielded many interesting products and indicated that more complex reactions were occurring than had been anticipated.

Treatment of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine LVIj with ten per cent hydrochloric acid yielded two products, neither of which gave a violet color with ethandic ferric chloride solution. This indicated that the hydroxamic acid grouping had been altered during the reaction. It was thought at first that the two products were 3,4-dihydro-3-oxo-2H-1,4-benzothiazine (XXXVII), and the corresponding sulfone, 3,4-dihydro-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (LXXIX). An internal oxidation-reduction reaction could explain the formation of both compounds (Scheme 42). Analytical data, infrared studies, and a comparison of melting points with those reported tended to confirm this theory. Pound (54) however, by means of mass spectral and NMR studies, determined that the product thought to be the sulfone

was, in fact, 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (LXXX). The mass spectrum showed a molecular ion at m/e 199 which satisfies a molecular formula of C_8H_6ClNOS. The signal ascribable to the aromatic protons in the NMR was complex, and was consistent with a 1,2,4-trisubstituted benzene derivative.

Methyl (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIe) was also treated with ten per cent aqueous hydrochloric acid. Two products were isolated from the reaction, one of which was identified as the lactam (6-bromo-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXI). The compound analyzed satisfactorily for $C_{10}H_8BrNO_3S$ and infrared data supported this structure. The second product obtained was subjected to mass spectral and NMR studies. Molecular ions of m/e 335, 337, and 339 with relative intensities of 19 per cent, 25 per cent, and seven per cent respectively were consistent (53) with the product being (6-bromo-7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXII). The presence of these three molecular ions of such relative intensities is explained by the existence of the isotopes ^{79}Br, ^{81}Br, ^{35}Cl and ^{37}Cl as indicated below:

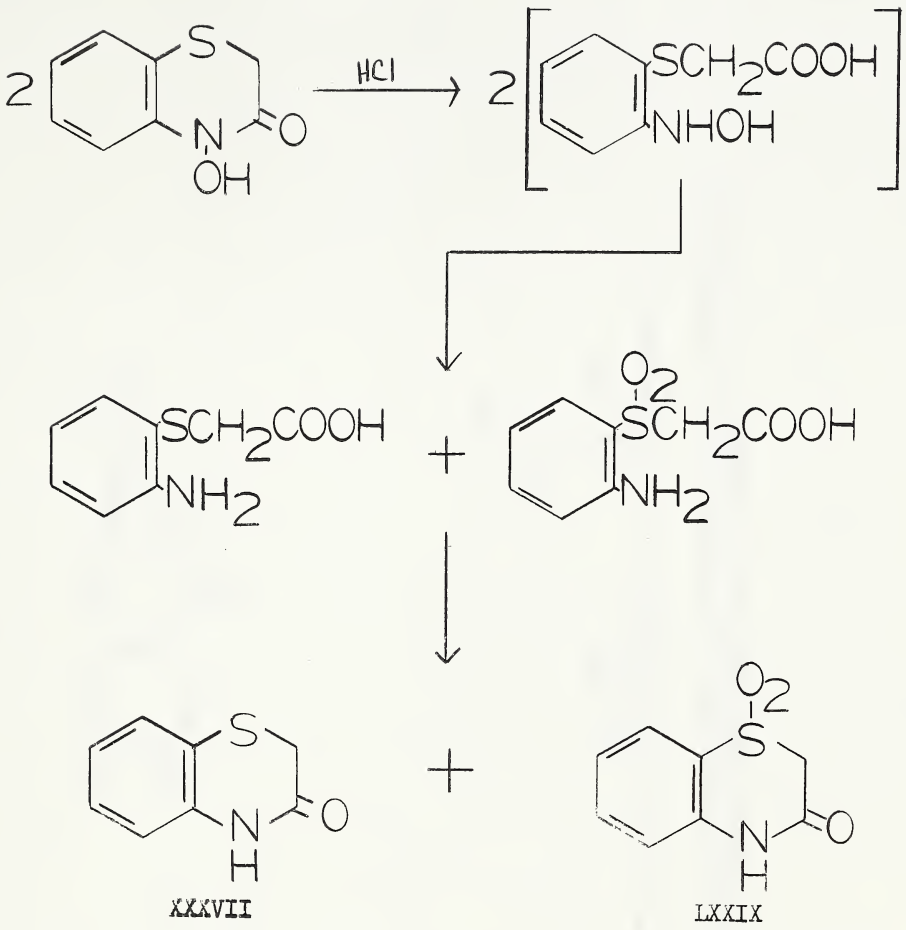
335: $C_{10}H_7{}^{79}Br{}^{35}ClNO_3S$

337: $C_{10}H_7{}^{79}Br{}^{37}ClNO_3S$

$C_{10}H_7{}^{81}Br{}^{35}ClNO_3S$

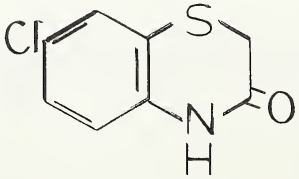
339: $C_{10}H_7{}^{81}Br{}^{37}ClNO_3S$

Also present in the mass spectrum were fragment ions of mass 321, 319, 317, 293, 291, and 289 (Figure 7). Formation of these ions is postu-



XXXVII LXXIX

Scheme 42



LXXX

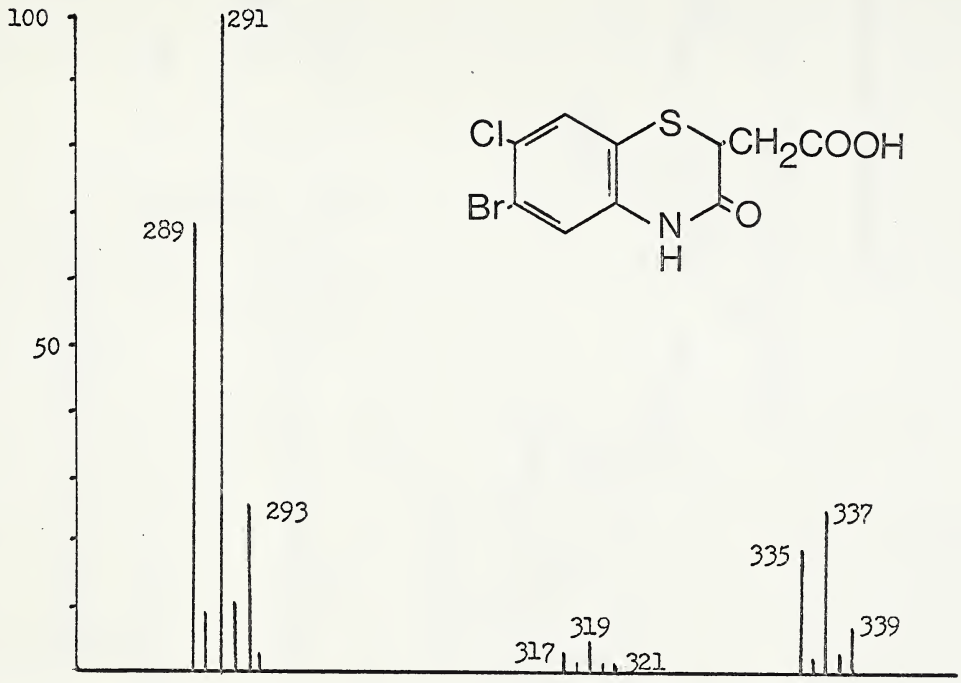
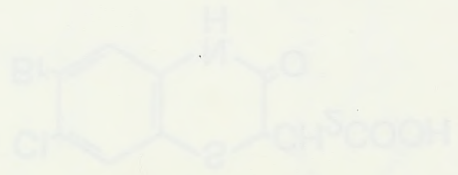
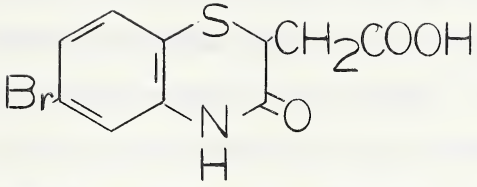


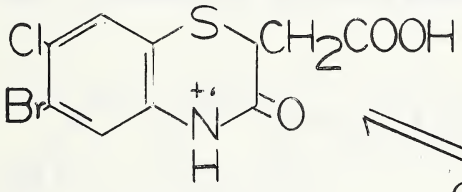
Figure 7: A portion of the mass spectrum of (6-bromo-7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXII).



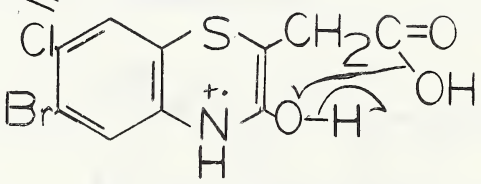


LXXXI

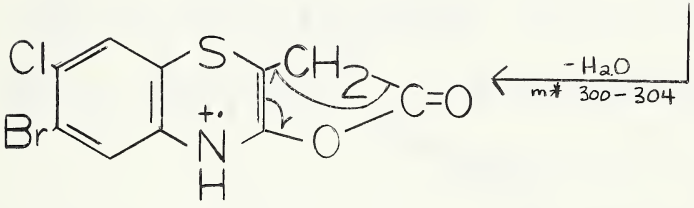
lated below (Scheme 43).



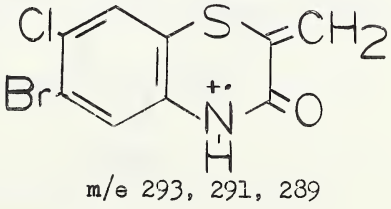
LXXXII



m/e 339, 337, 335



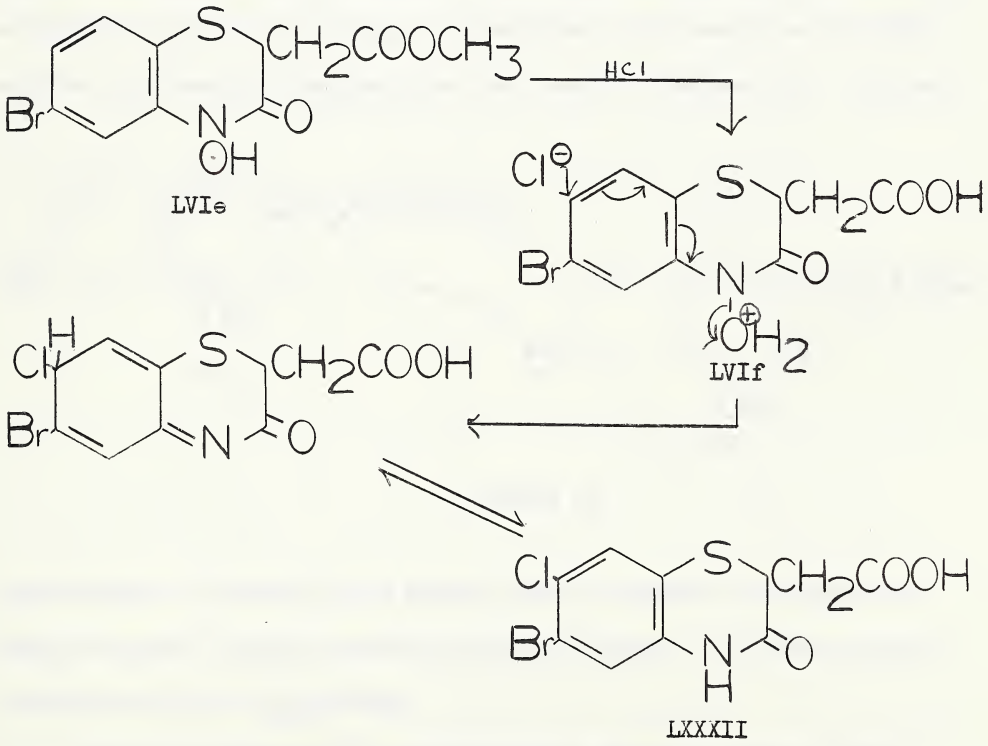
m/e 321, 319, 317



m/e 293, 291, 289

Scheme 43

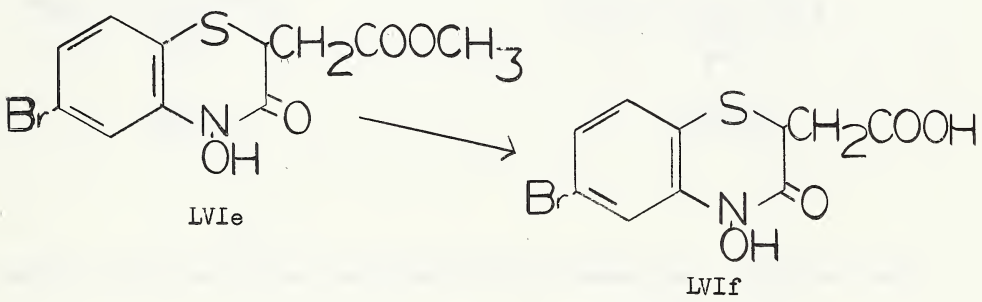
In addition, two 1-proton singlets located at τ2.33 and τ2.67 in the NMR spectrum of this compound indicated that the two hydrogen atoms in the aromatic ring were in positions <u>para</u> to one another. The two protons would be expected to be nonequivalent due to the different deshielding properties of the N and S atoms in the hetero ring. As with the preparation of 7-chloro-3,4-dihydro-3-oxo-2<u>H</u>-1,4-benzothiazine, formation of LXXXII is explained by nucleophilic attack of Cl^- ion on the hydroxamic acid LVIf and subsequent loss of the hydroxyl group (Scheme 44). Treatment of LVIe with methanolic hydrochloric acid, however,



Scheme 44

yielded only starting material, even when the time of heating was increased to two hours. The ester side chain would not be expected to be hydrolyzed under these conditions, and this would seem to indicate that the acid function must be present in the side chain before conditions are favorable for attack of the Cl^- ion.

Four of the 2H-1,4-benzothiazine hydroxamic acids were also treated with ten per cent sodium hydroxide solution. Methyl (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIe) was allowed to stand in ten per cent sodium hydroxide solution at room temperature for 43 hours. The corresponding acid, (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LVIf), was the only product isolated from the reaction (Scheme 45). It was



LVIe LVIf

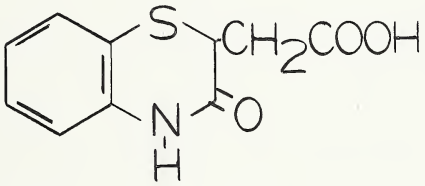
Scheme 45

characterized by means of the purple color it formed with ethanolic ferric chloride solution, and by infrared studies. It also analyzed satisfactorily for $C_{10}H_8BrNO_4S$.

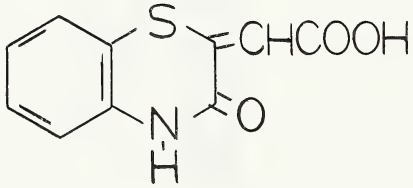
When the compounds were heated under reflux in ten per cent sodium hydroxide solution, however, the reaction became much more

complex. None of the products gave a violet color with ethanolic ferric chloride solution, indicating that the hydroxamic acid grouping had not survived the reaction.

(3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LVIa) was treated in this manner. Two of the products of the reaction were identified. They were (3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (XXXVIIb) and 3,4-dihydro-3-oxo-2H-1, 4-benzothiazin-$\Delta^{2,\alpha}$-acetic acid (XXXVIIc). The lactam XXXVIIb was characterized by means of elemental analysis and comparison of its



XXXVIIb



XXXVIIc

melting point with that reported in the literature. Infrared data also supported this structure. Compound XXXVIIc analyzed satisfactorily for $C_{10}H_7NO_3S$ and the mass spectrum showed a molecular ion at m/e 221. Also present in the mass spectrum were $(m\text{-}OH)^+$, $(m\text{-}H_2O)^+$, and $(m\text{-}CO_2)^+$, $(m\text{-}COOH)^+$ and $(m\text{-}CO_2H_2)^+$ fragment ions at m/e 204, 203, 177, 176 and 175 respectively (Figure 8). The presence of an absorption band at 1670 cm^{-1} in the infrared spectrum of this compound is consistent with an α,β-unsaturated acid function. A

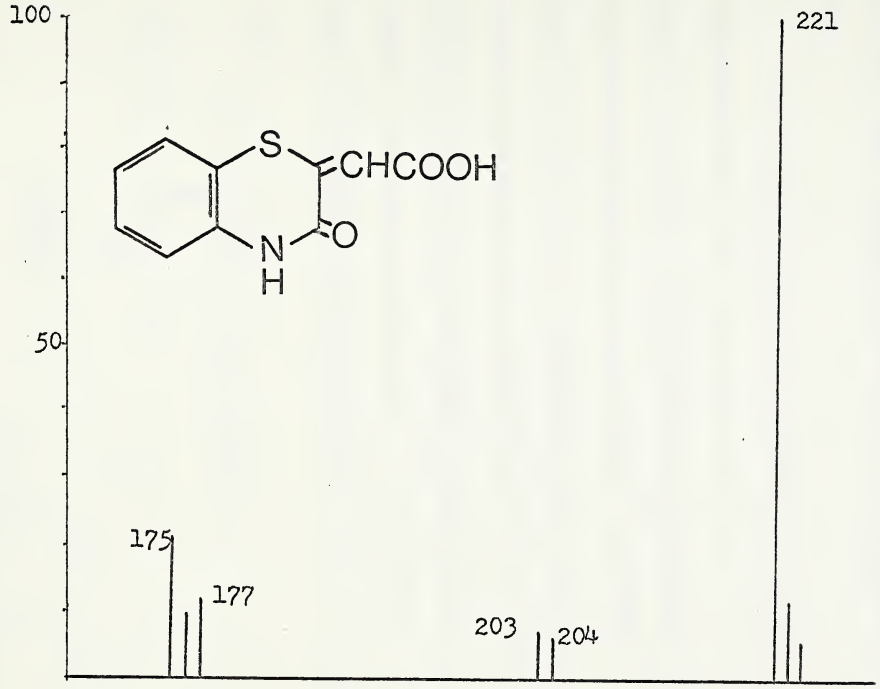
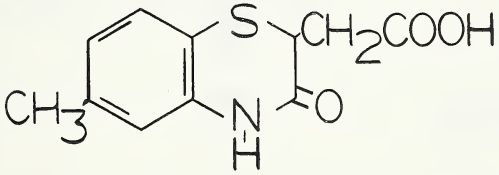


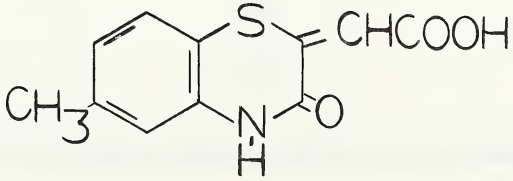
Figure 8: A portion of the mass spectrum of 3,4-dihydro-3-oxo-2H-1,4-bensothiazine-$\Delta^{2,\alpha}$-acetic acid (XXXVIIc).

search of the literature showed this compound to be known, and accordingly it was prepared by the alternative method of Muskalo and Brezemskaeja (38) for comparison purposes. o-Aminothiophenol and acetylene dicarboxylic acid were dissolved in ether and XXXVIIc immediately precipitated as a yellow powder. The infrared spectra of these compounds were identical and the melting points were very close.

(6-Methyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LVId) was also heated with ten per cent sodium hydroxide solution. Two products were isolated from the reaction and have been assigned structures LXXXIII and LXXXIV. Neither product formed a purple color in ethanolic ferric chloride solution, indicating that the hydroxamic acid grouping had not survived the reaction. (6-Methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXIII) analyzed indifferently for $C_{11}H_{11}NO_3S$; however, the presence of absorption bands at 1670 and 1700 cm^{-1} characteristic of



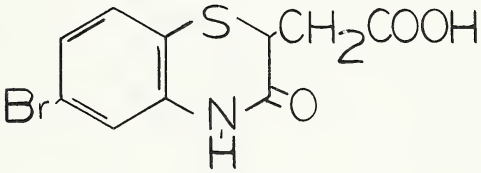
LXXXIII



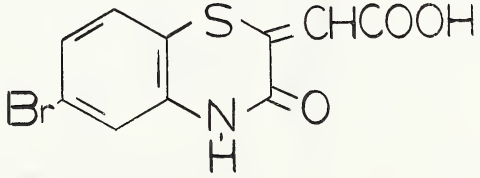
LXXXIV

amide and acid carbonyl functions (56) and of broad OH and NH absorption bands in the infrared spectrum support this structure. Structure LXXXIV has been assigned to the second product in view of mass spectral and infrared evidence. A peak at 1659 cm^{-1} in the infrared spectrum is characteristic of an α,β-unsaturated acid function (56). The compound analyzed satisfactorily for $C_{11}H_9NO_3S$ and its mass spectrum showed a molecular ion at m/e 235 and fragment ions at m/e 191, 190 and 189 (Figure 9), similar to the fragment ions observed in the lower homolog (Figure 8).

Methyl (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIe) was also treated with boiling ten per cent sodium hydroxide solution. One product of the reaction, (6-bromo-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXI) was identified by means of elemental analysis and infrared spectral studies.



LXXXI



LXXXV

It was identical with the non-chlorinated product obtained from treatment of LVIe with ten per cent hydrochloric acid. A second product was presumed to be 6-bromo-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-

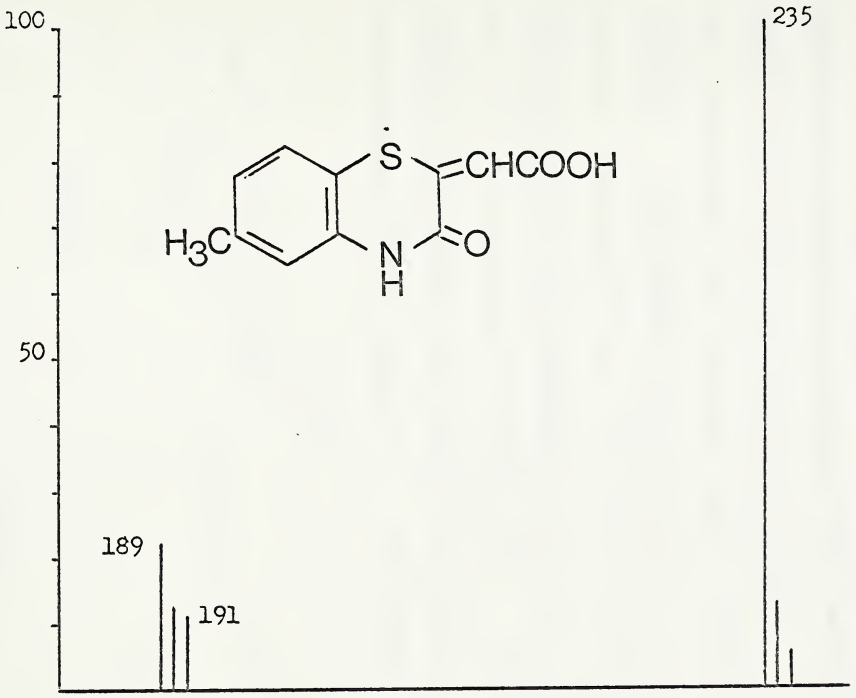
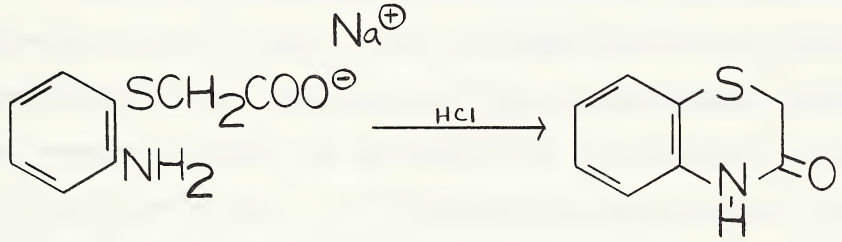


Figure 9: A portion of the mass spectrum of 6-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetic acid (LXXXIV).

$\Delta^{2,\alpha}$-acetic acid (LXXXV). This product was very difficult to recrystallize and analyzed indifferently for $C_{10}H_6BrNO_3S$. An absorption band at 1665 cm^{-1} in its infrared spectrum was suggestive of an α,β-unsaturated acid carbonyl function. The third product of the reaction was not identified.

The simpler parent benzothiazine hydroxamic acid, 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (LVIj) was also treated with boiling ten per cent sodium hydroxide solution. A high melting solid precipitated from the basic reaction mixture prior to its acidification. This compound has been identified as the salt (LXXXVI). Absorption bands at 1635 and 1363 cm^{-1} in the infrared spectrum are characteristic of the carboxylate ion (56), and a strong peak at 3410 cm^{-1} can be ascribed to the NH_2 group. Acidification of a solution of this sodium salt yielded 3,4-dihydro-3-oxo-2H-1,4-benzothiazine (XXXVII) (Scheme 46). The filtrate remaining after

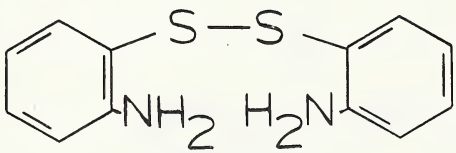


LXXXVI XXXVII

Scheme 46

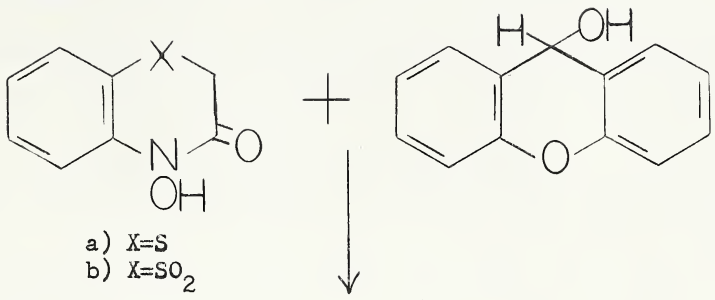
removal of LXXXVI was acidified to yield two products. One of the products was identified as the lactam (XXXVII) by means of its melting

point and by comparison of its infrared spectrum with that of an authentic sample (45). The other product was a high melting solid which was only partially soluble in ten per cent sodium hydroxide solution. The soluble fraction was mainly inorganic and was not investigated further. The insoluble fraction was 2,2'-diaminodiphenyldisulfide (LXXV). It was identical with the product described earlier which was obtained from the reduction of ethyl α-benzoyl-α-(o-nitrophenylthio)acetate (LIIId).

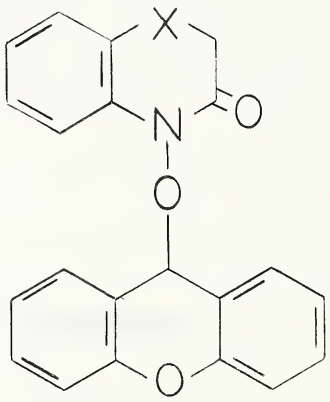


LXXXV

An attempt was made to characterize cyclic benzothiazine hydroxamic acids by means of their xanthenyl derivatives (Scheme 47). 3,4-Dihydro-3-oxo-4-(9-xanthenyloxy)-2H-1,4-benzothiazine (LXXXVII a) was prepared by adding the hydroxamic acid to a solution of xanthydrol in glacial acetic acid. A colorless crystalline derivative was obtained. Elemental analysis was satisfactory for a molecular formula of $C_{21}H_{15}NO_3S$ and the infrared spectrum indicated the absence of an OH stretching band and the presence of a peak at 1691 cm^{-1}. The derivative, therefore, was assigned structure LXXXVIIa. In the same way, 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine 1,1-dioxide



a) X=S
b) X=SO_2



LXXXVIII

a) X=S
b) X=SO_2

Scheme 47

was converted into its xanthenyl derivative (LXXXVII b). Attempts to recrystallize this compound resulted in decomposition. The infrared spectrum showed a carbonyl peak at 1698 cm^{-1}; O-H absorption was not observed. Other cyclic benzothiazine hydroxamic acids were reacted with xanthydrol but no crystalline derivatives were obtained due to decomposition.

EXPERIMENTAL

1.0.0. General Comments

Infrared spectra were recorded on a Unicam SP200 spectrophotometer, a Unicam SP200G spectrophotometer, a Beckman I.R. 5 spectrophotometer, or a Beckman I.R. 10 spectrophotometer.

NMR spectra were recorded in tau (τ) values on a Varian A-60D spectrophotometer. Tetramethylsilane (TMS) was the reference.

Mass spectra were recorded on an A.E.I. MS9 instrument equipped with a heated inlet system; the electron beam energy was 70 ev.

Melting points were uncorrected.

2.0.0. Condensation of substituted o-chloro- or o-bromonitrobenzenes with mercaptosuccinic acid or thioglycolic acid.

2.1.0. General Method.

The substituted o-chloro- or o-bromonitrobenzene (0.1 mole) was heated under reflux for four to six hours with mercaptosuccinic or thioglycolic acid (0.1 mole) in 50 per cent aqueous ethanol (200 ml.) in which had been suspended sodium bicarbonate (0.3 moles). The reaction mixture was then cooled, flooded with water and acidified with concentrated hydrochloric acid. The precipitate which formed was removed by filtration. Additional product was obtained by extracting the filtrate with ether, re-extracting the ether layer with ten per cent sodium hydroxide solution and acidifying the basic layer with concentrated hydrochloric acid.

The identity of each product was confirmed by a comparison of its infrared spectrum with that of an authentic sample. The products were used in subsequent reactions without further purification.

2.1.1. α-(o-Nitrophenylthio)succinic acid (LIa).

Using general method 2.1.0., the interaction of o-chloronitrobenzene (14 g.) and mercaptosuccinic acid (15 g.) for five hours gave the title compound (50-60 per cent yield) as a yellow powder, m.p. 185-186°. Lit. (43) m.p. 187-189°.

Infrared spectrum (KBr disc): 1695(s)(C=O); 1515(s), 1345(s)(NO_2); 2990(m,broad)(OH) cm^{-1}.

2.1.2. α-(4-Bromo-2-nitrophenylthio)succinic acid (LIb).

The interaction of 2,5-dibromonitrobenzene (28 g.) and mercaptosuccinic acid (15 g.) for four hours, using general method 2.1.0., gave the title compound (90-95 per cent yield) as a yellow powder, m.p. 210-215°. Lit. (43) m.p. 218-220°.

Infrared spectrum (KBr disc): 1710(s)(C=O); 1525(s), 1345(s) (NO_2); 3000(m,broad)(OH) cm^{-1}.

2.1.3. α-(4-Methyl-2-nitrophenylthio)succinic acid (LIc).

Using general method 2.1.0., the interaction of 4-chloro-3-nitrotoluene (17 g.) and mercaptosuccinic acid (15 g.) for four hours gave the title compound (35-45 per cent yield) as a yellow powder, m.p. 212-215°. Lit. (43) m.p. 215-218°.

Infrared spectrum (KBr disc): 1700(s)(C=O); 1530(s), 1340(s) (NO_2); 2950(s,broad)(OH) cm^{-1}.

2.1.4. α-(4-Trifluoromethyl-2-nitrophenylthio)succinic acid (LId).

The interaction of 2-chloro-5-trifluoromethylnitrobenzene (22.5 g.) and mercaptosuccinic acid (15 g.) for four hours, using general method 2.1.0., gave the title compound (65-80 per cent yield) as a yellow powder, m.p. 196-197°. Lit. (43) m.p. 196-198°.

Infrared spectrum (KBr disc): 1710(s)(C=O); 1545(s), 1350(s) (NO_2); 2875(m,broad)(OH) cm^{-1}.

2.1.5. ∝-(4-Chloro-2-nitrophenylthio)succinic acid (LIe).

Using general method 2.1.0., the interaction of 2,5-dichloronitrobenzene (19 g.) and mercaptosuccinic acid (15 g.) for three hours gave the title compound (50 per cent yield) as a yellow powder, m.p. 212.5-214° (aq. EtOH).

Infrared spectrum (KBr disc): 1705(s), 1715(s)(C=O); 1520(s), 1337(s), 880(m)(NO_2); 3080(s,broad)(OH) cm^{-1}.

Anal. $C_{10}H_8ClNO_6S$ requires: C, 39.29; H, 2.64; N, 4.58 per cent.

Found: C, 39,75; H, 2.82; N, 4.50 per cent.

2.1.6. ∝-(o-Nitrophenylthio)acetic acid (LIf).

By employing general method 2.1.0., o-chloronitrobenzene (31.5 g.) and thioglycolic acid (18.5 g.) were interacted for 2.5 hours, and gave the title compound (70 per cent yield) as a yellow powder, m.p. 160-163°. Lit. (36) m.p. 164°.

Infrared spectrum (nujol mull): 1713(s)(C=O); 1510(s), 1335(s), 875(m)(NO_2); 3300-2400(m)(OH) cm^{-1}.

3.0.0. Preparation of methyl ∝-(o-nitrophenylthio)esters.

3.1.0. General Method.

The ∝-(o-nitrophenylthio)acid (10 g.) was heated under reflux for 15 hours in methanol (100 ml.) to which had been added concentrated sulfuric acid (10 ml.). The reaction mixture was cooled and if the

ester did not precipitate, the solution was flooded with water and extracted with ether. The ether layer was re-extracted with ten per cent sodium hydroxide solution to remove any unreacted acid, washed with water, then dried (Na_2SO_4), and evaporated to yield the ester.

3.1.1. Dimethyl α-(o-nitrophenylthio)succinate.(LIg).

Using general method 3.1.0., the title compound was obtained as a brown oil (70-80 per cent yield) from α-(o-nitrophenylthio)succinic acid. This ester is described in literature (43) as an orange oil.

Infrared spectrum (thin film): 1727(s), 1720(s)(C=O); 1530(s), 1350(s), 875(s)(NO_2) cm^{-1}.

3.1.2. Dimethyl α-(4-methyl-2-nitrophenylthio)succinate(LIi).

Using general method 3.1.0., the title compound was obtained as a yellow oil (70-80 per cent yield) from α-(4-methyl-2-nitrophenylthio)succinic acid. The oil, on trituration with methanol, gave yellow crystals, m.p. 49-50°. This product is described in literature (43) as a brown oil.

Infrared spectrum (KBr disc): 1740(s), 1737(s)(C=O); 1545(s), 1353(s), 860(w)(NO_2) cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_6S$: C,49.83; H, 4.82; N, 4.47 per cent.

Found: C, 49.72; H, 5.02; N, 4.52 per cent.

3.1.3. Dimethyl α-(4-bromo-2-nitrophenylthio)succinate (LIh).

The title compound (55-60 per cent yield) was obtained from

∝-(4-bromo-2-nitrophenylthio)succinic acid as an orange oil, using general method 3.1.0. The oil, on trituration with methanol, gave yellow crystals, m.p. 68-71°. Lit. (43) m.p. 70-71°.

Infrared spectrum (KBr disc):1750(s)(C=O); 1520(s), 1330(s), 870(m)(NO_2) cm^{-1}.

3.1.4. Dimethyl ∝-(4-trifluoromethyl-2-nitrophenylthio)succinate (LIj).

The title compound (70-80 per cent yield) was obtained from ∝-(4-trifluoromethyl-2-nitrophenylthio)succinic acid as a brown oil, using general method 3.1.0. The oil, on trituration with methanol, gave cream-colored crystals, m.p. 50-54°. Lit. (26) m.p. 47°.

Infrared spectrum (KBr disc): 1730(s)(C=O); 1540(s), 1340(s), 850(w)(NO_2) cm^{-1}.

3.1.5. Dimethyl ∝-(4-chloro-2-nitrophenylthio)succinate (LIk).

Using general method 3.1.0., the title compound (66 per cent yield) was obtained from ∝-(4-chloro-2-nitrophenylthio)succinic acid as yellow crystals, m.p. 73-75° (EtOH).

Infrared spectrum (KBr disc): 1740(s), 1750(s)(C=O); 1517(s), 1335(s), 875(m)(NO_2) cm^{-1}.

Anal. $C_{12}H_{12}ClNO_6S.\frac{1}{2}EtOH$ requires: C, 43.80; H, 4.23 per cent.
Found: C, 44.00; H, 3.75 per cent.

3.1.6. Methyl ∝-(o-nitrophenylthio)acetate (LIm).

The title compound (85-90 per cent yield) was obtained from

(o-nitrophenylthio)acetic acid as yellow needles, m.p. 89-90°, using general method 3.1.0. Lit.(36) m.p. 89-90°.

Infrared spectrum (KBr disc): 1730(s)(C=O); 1515(s), 1350(s), 850(m)(NO_2) cm^{-1}.

4.0.0. Preparation of hydroxamic acids from substituted α-(o-nitrophenylthio)esters.

4.1.0. General Method.

A solution of sodium borohydride (1.0 g.) in water (5 ml.) was added to a suspension of palladium (ten per cent)-on-charcoal (0.1 g.) in water (5 ml.). Dioxane (5 ml.) was added to the mixture and nitrogen gas bubbled through it (one-two minutes). The substituted α-(o-nitrophenylthio)ester (1.0 g.), dissolved in a minimum of dioxane, was added to the reduction mixture dropwise over a period of 15-30 minutes. Nitrogen gas was bubbled through the reaction mixture during the addition of ester and for an additional 15 minutes.

The reaction mixture was filtered and the charcoal washed with portions of water and dioxane. The washings were added to the filtrate and the filtrate acidified with concentrated hydrochloric acid, keeping the temperature below 30°. The solid hydroxamic acid which precipitated was removed by filtration. Additional product was obtained by extraction of the filtrate with ether, re-extracting the ether layer with ten per cent sodium hydroxide solution and acidifying the basic layer with concentrated hydrochloric acid, keeping the temperature below 30°. If no precipitate formed, the acidic solution was extracted

with ether, the ether layer was dried (Na_2SO_4), and evaporated to yield the hydroxamic acid.

If no precipitate formed when the original filtrate was acidified, the acidified filtrate was subjected to the same extraction procedure as that described immediately above.

4.1.1. Attempted preparation of methyl (3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIa).

Using general method 4.1.0., dimethyl α-(o-nitrophenylthio)-succinate (LIg)(3.0 g.) was reduced to give a grey product (1.5 g.), m.p. 189.5-192°(aq. MeOH), which was not the title compound (Lit. (43) m.p. 122-124°), but was (3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LVIb). Lit. (45) m.p. 186-188°.

Infrared spectrum (KBr disc): 1640(s)(hydroxamate C=O); 1690(s) (acid C=O); 3300(s,broad)(hydrogen bonded OH) cm^{-1}.

4.1.2. Attempted preparation of methyl (6-methyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIc).

Using general method 4.1.0., dimethyl α-(4-methyl-2-nitrophenylthio)succinate (LIi) (2 g.) was reduced to give a pale yellow product (0.7 g.), m.p. 187-188°, which was not the title compound (Lit. (43) m.p. 96-97°), but was (6-methyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LVId).

Infrared spectrum (KBr disc): 1650(s)(hydroxamate C=O); 1685(s) (acid C=O); 3000(s,broad)(hydrogen bonded OH) cm^{-1}.

Anal. $C_{11}H_{11}NO_4S$ requires: C, 52.16; H, 4.38 per cent.

Found: C, 52.44; H, 4.44 per cent.

4.1.3. Preparation of methyl (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIe).

Using general method 4.1.0., dimethyl ∝-(4-bromo-2-nitrophenylthio)succinate (LIh) was reduced to give the title hydroxamic acid as a white powder (65 per cent yield), m.p. 159-161°. Lit. (43) m.p. 165-167°.

Infrared spectrum (KBr disc): 1740(s), 1665(s)(C=O); 3450(m, broad)(OH) cm^{-1}.

4.1.4. Attempted preparation of methyl (6-trifluoromethyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIg).

Using general method 4.1.0., dimethyl ∝-(4-trifluoromethyl-2-nitrophenylthio)succinate (LIj)(2.0 g.) was reduced to give a white crystalline product (0.7 g.), m.p. 182-184°, which was not the title compound (Lit.(43) m.p. 123-125°), but was (6-trifluoromethyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LVIh). Lit. (45) m.p. 178-180°.

Infrared spectrum (KBr disc): 1650(s)(hydroxamate C=O); 1690(s) (acid C=O); 3300(m,broad)(hydrogen bonded OH) cm^{-1}.

4.1.5. Preparation of methyl (6-chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIi).

Using general method 4.1.0., dimethyl ∝-(4-chloro-2-nitro-

phenylthio)succinate (LIk) was reduced to give the title hydroxamic acid as white crystals (76 per cent yield), m.p. 157-159° (EtOH).

Infrared spectrum (KBr disc): 1660(s)(hydroxamate C=O); 1740(s) (ester C=O); 3160(m,broad)(hydrogen bonded OH) cm^{-1}.

Anal. $C_{11}H_{10}ClNO_4S$ requires: C, 45.91; H, 3.50 per cent.
Found: C, 46.32; H, 3.67 per cent.

4.1.6. Preparation of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (LVIj).

Using general method 4.1.0., methyl α-(o-nitrophenylthio)-acetate (LIm) was reduced to give the title hydroxamic acid as white crystals (40-45 per cent yield) m.p. 148-150°(benzene). Lit. (45) m.p. 151-152°.

Infrared spectrum (KBr disc): 1680(s), 1625(s)(C=O); 3200-2800(m)(OH) cm^{-1}.

5.0.0. Action of hydrochloric acid on 2H-1,4-benzothiazine hydroxamic acids.

5.1.0. Acid treatment of 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (LVIj).

5.1.1. Aqueous Hydrochloric Acid.

The hydroxamic acid (0.9 g.) was suspended in ten per cent hydrochloric acid (30 ml.) and heated under reflux for 0.5 hour. The hydroxamic acid failed to dissolve but after ten minutes of heating, the solution was a dark green color and the crystalline structure of the

suspended material had altered in appearance. The hot reaction mixture was filtered to give product A (0.58 g.). The filtrate was cooled and product B (0.06 g.) precipitated. Product C (0.04 g.) precipitated when the filtrate from product B was allowed to stand overnight. The final filtrate was then extracted with ether, the ether solution was dried (Na_2SO_4) and evaporated to yield product D (0.07 g.).

None of the products gave a violet color with ethanolic ferric chloride solution.

Products A and B had identical infrared spectra. These two products were combined and recrystallized from methanol to give 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (LXXX) as a white solid, m.p. 206-207.5°.

Infrared spectrum(KBr disc): 1684(s)(C=O); 3074(m)(NH) cm^{-1}.

Anal. Calc'd. for C_8H_6ClNOS: C, 48.12; H, 3.03; N, 7.01 per cent.
Found: C, 47.75; H, 3.14; N, 6.97 per cent.

Products C and D had similar infrared spectra. They were combined and recrystallized from methanol to give 3,4-dihydro-3-oxo-2H-1,4-benzothiazine (XXXVII) as a white solid, m.p. 175-176°. Lit. (60) m.p. 179°.

Infrared spectrum (KBr disc): 1661(s)(C=O); 3208(m)(NH) cm^{-1}.

Anal. Calc'd. for C_8H_7NOS: C, 58.16; H, 4.27 per cent.
Found: C, 57.83; H, 4.06 per cent.

5.1.2. Methanolic Hydrochloric Acid.

The title hydroxamic acid (0.99 g.) was dissolved in methanol

(20 ml.), concentrated hydrochloric acid (10 ml.) was added dropwise to avoid local overheating, and the solution heated under reflux for 0.5 hour. After ten minutes of heating, the solution was a dark green color and a solid started to precipitate out. The hot reaction mixture was filtered to give product A (0.34 g.). The filtrate was cooled and product B (0.27 g.) precipitated. Product C (0.1 g.) precipitated when the filtrate from product B was allowed to stand overnight. The filtrate from product C was then flooded with water and product D (0.13 g.) precipitated. The final filtrate was then extracted with ether, the ether solution was dried (Na_2SO_4) and evaporated to yield product E (0.1 g.).

None of these products gave a violet color with ethanolic ferric chloride solution.

Products A, B and C had identical infrared spectra. They were combined and recrystallized from methanol to give 7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (LXXX) as a white powder, m.p. 206-208°, which had an infrared spectrum identical with that of the product described in section 5.1.1.

Products D and E gave very similar infrared spectra. They were combined and recrystallized from methanol to give 3,4-dihydro-3-oxo-2H-1,4-benzothiazine (XXXVII) as a white solid, m.p. 175-176°, which had an infrared spectrum identical to that of the product described in section 5.1.1.

5.2.0. Acid treatment of methyl (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIe).

5.2.1. Aqueous Hydrochloric Acid.

The title hydroxamic acid (1.0 g.) was suspended in ten per cent hydrochloric acid (30 ml.) and heated under reflux for 0.5 hour. The hydroxamic acid failed to dissolve but the solution turned a yellow color and the crystalline structure of the suspended material altered in appearance. The hot reaction mixture was filtered to give product A (0.408 g.). The filtrate was then cooled and product B (0.33 g.) precipitated. The filtrate from product B was then extracted with ether, the ether solution dried (Na_2SO_4), and evaporated to yield product C (0.07 g.).

None of these products gave a violet color with ethanolic ferric chloride solution.

Products A and B had similar infrared spectra. These two products were combined and recrystallized from ethanol to give (6-bromo-7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXII) as a white solid, m.p. 269-271°.

Infrared spectrum (KBr disc): 1643(s), 1689(s), 1700(s)(C=O); 3181(m)(NH) cm^{-1}.

Anal.: $C_{10}H_7BrClNO_3S$ requires: C, 35.67; H, 2.09; N, 4.16; S, 9.52 per cent.

Found: C, 35.69; H, 2.17; N, 4.01; S, 9.77 per cent.

Mass spectrum: 339(7), 337(25), 335(19); 321(1.5), 319(5), 317(3.5); 293(25), 291(100), 289(68); m/e(rel. abund. per cent). Numerous other peaks of m/e less than 289 were also present in the spectrum.

NMR(in DMSO-D_6): 2.33, 2.67 (1-proton singlets) (2 para substituted ring protons). Other signals were also present in the spectrum.

The filtrate remaining after removal of the above product from the recrystallization solution was flooded with water to give a white solid which had an infrared spectrum identical with that of product C. These two products were combined and recrystallized from aqueous ethanol to give (6-bromo-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)-acetic acid (LXXXI) as a white solid, m.p. 251-253°.

Infrared spectrum (KBr disc): 1707(s), 1663(s)(C=O); 3178(m) (NH); 3500-2800(m) (OH) cm^{-1}.

Anal.: $C_{10}H_8BrNO_3S$ requires: C, 39.75; H, 2.67; N, 4.64; S, 10.61 per cent.

Found: C, 39.49; H, 2.68; N, 4.72; S, 10.52 per cent.

5.2.2. Methanolic Hydrochloric Acid.

The hydroxamic acid (0.99 g.) was dissolved in methanol (20 ml.), concentrated hydrochloric acid (10 ml.) was added dropwise to avoid local overheating and the solution heated under reflux for 0.75 hour. The only product isolated from this reaction was the unreacted,

title hydroxamic acid.

The reaction was repeated, except that the heating of the reaction mixture under reflux was continued for two hours. Starting material was the only product isolated.

6.0.0. Alkaline Hydrolysis of 2H-1,4-Benzothiazine Hydroxamic Acids.

6.1.0. 3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LVIb).

The title hydroxamic acid (1.6 g.) was dissolved in ten per cent sodium hydroxide (50 ml.) and heated under reflux for one hour. The dark red reaction mixture was cooled and acidified carefully with concentrated hydrochloric acid and product A (0.927 g.) precipitated. The filtrate was allowed to stand and product B (0.08 g.) precipitated. The filtrate from product B was then extracted with ether, the ether layer dried (Na_2SO_4), and evaporated to yield product C (0.25 g.).

None of these products gave a violet color with ethanolic ferric chloride solution.

Product A was repeatedly recrystallized from methanol to give 3,4-dihydro-3-oxo-2H-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetic acid (XXXVIIc) as a yellow-green powder, m.p. 280-282°. Lit. (38) m.p. 278°(d).

Anal. Calc'd. for $C_{10}H_7NO_3S$: C, 54.29;
H, 3.19; N, 6.33 per cent, mol. wt. 221.
Found: C, 54.49; H, 3.49; N, 6.52 per cent,
mol. wt. (mass spectrum), 221.

The infrared spectrum was identical with that of an authentic sample, prepared as described in section 6.1.1.

Product C was recrystallized from aqueous methanol to give (3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (XXXVIIb) as a white powder, m.p. 189-191°. Lit. (37) m.p. 195-196°.

Infrared spectrum (KBr disc): 1665(s)(amide C=O);1695(s)(acid C=O); 3200(m)(NH) cm^{-1}.

Anal. Calc'd for $C_{10}H_9NO_3S$: C, 53.79;
H, 4.06; N, 6.27, S, 14.36 per cent,

Found: C, 53.60; H, 4.07; N, 6.42; S, 13.88 per cent.

Minor product B was not investigated further.

6.1.1. Preparation of 3,4-dihydro-3-oxo-2H-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetic acid (XXXVIIc) (38).

o-Aminothiophenol (1.008 g.) was dissolved in diethyl ether (10 ml.) and added, with stirring, to a solution of acetylene dicarboxylic acid (0.924 g.) in diethyl ether (20 ml.). The title compound (75 per cent) precipitated as a yellow powder, m.p. 277-279°(d). Lit. (38) m.p. 278°(d).

Infrared spectrum (KBr disc): 1670(s)(α,β-unsat'd C=O); 3300-2800(s)(OH,NH) cm^{-1}.

6.2.0. (6-Methyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LVId).

The title hydroxamic acid (1 g.) was dissolved in ten per cent sodium hydroxide (50 ml.) and heated under reflux for one hour. The reaction mixture was cooled and acidified carefully with concentrated hydrochloric acid to precipitate product A (0.291 g.). The filtrate was allowed to stand and product B (0.333 g.) precipitated and was removed. Extraction of the resulting filtrate with ether yielded only a negligible amount of product, which was discarded.

Neither of the products A or B gave a violet color with ethanolic ferric chloride solution.

Product A was recrystallized from methanol to yield 6-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetic acid (LXXXIV) as a yellow powder, m.p. 307-309°(d).

Infrared spectrum (KBr disc): 1659(s)(α,β-unsat'd C=O); 3300-2700(s)(OH,NH) cm^{-1}.

Anal. $C_{11}H_9NO_3S$ requires: C, 56.16; H, 3.86; N, 5.95 per cent
mol. wt. 235.

Found: C, 55.66; H, 3.90; N, 5.57 per cent
mol. wt. (mass spectrum) 235.

Product B was recrystallized from methanol to give what was presumed to be (6-methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)-acetic acid (LXXXIII) as a cream colored powder, m.p. 237-239°.

Infrared spectrum (KBr disc): 1670(s)(amide C=O); 1700(s)(acid C=O); Broad absorption 2800-3300(m)(OH) with maximum at 3280 (m) (NH) cm^{-1}.

The product analysed indifferently for $C_{11}H_{11}NO_3S$:

Anal. $C_{11}H_{11}NO_3S$ requires: C, 55.68; H, 4.67; N, 5.90 per cent.
Found: C, 56.74; H, 4.57; N, 4.37 per cent.

6.3.0. Methyl (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIe).

6.3.1. Room temperature.

The title compound hydroxamic acid (0.55 g.) was dissolved in ten per cent sodium hydroxide (30 ml.) and the solution allowed to stand at room temperature for 43 hours. The solution was clarified by filtration and the filtrate acidified carefully with concentrated hydrochloric acid to precipitate (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LVIf) as a cream colored solid (0.31 g.) m.p. 215-217° (MeOH).

This product gave a violet color with ethanolic ferric chloride solution.

Infrared spectrum (KBr disc): 1643(s)(hydroxamate C=O); 1700(s)(acid C=O); 3200(s,broad)(OH) cm^{-1}.

Anal. $C_{10}H_8BrNO_4S$ requires: C, 37.75; H, 2.52; N, 4.40; S, 10.07 per cent.
Found: C, 37.91; H, 2.63; N, 4.41; S, 9.66 per cent.

6.3.2. Elevated temperature.

The hydroxamic acid (2.3 g.) was dissolved in ten per cent sodium hydroxide solution (100 ml.) and heated under reflux for 0.75 hour. The reaction mixture was cooled and acidified carefully with concentrated hydrochloric acid and product A (1.5 g.) precipitated. The filtrate was allowed to stand and product B (0.479 g.) precipitated as a pale yellow solid. The filtrate from product B was then extracted with ether, the ether layer dried (Na_2SO_4) and evaporated to yield product C (0.169 g.) as a brown solid.

None of these products gave a violet color with ethanolic ferric chloride solution.

Product A was repeatedly recrystallized from aqueous methanol to give what was presumed to be 6-bromo-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetic acid as an orange powder (LXXXVI), m.p. 244-46°.

Infrared spectrum (KBr disc): 1665(s)(α,β-unsat'd C=O); 3400-2800(m)(OH) cm^{-1}.

The product analyzed indifferently for $C_{10}H_6BrNO_3S$:

Anal: $C_{10}H_6BrNO_3S$ requires: C, 40.02; H, 2.02; N, 4.67 per cent. Found: C, 38.96; H, 2.28; N, 5.09 per cent.

Product B was recrystallized from methanol to give (6-bromo-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXI) as a white powder, m.p. 251-53°.

Infrared spectrum(KBr disc): 1707(s), 1663(s)(C=O); 3178(m)(NH) cm^{-1}.

Anal. $C_{10}H_8BrNO_3S$ requires: C, 39.75; H, 2.67; N, 4.64; S, 10.61 per cent.

Found: C, 39.49; H, 2.68; N, 4.72; S, 10.52 per cent.

Product C, m.p. 269-272°, was a brown powder.

Infrared spectrum (KBr disc): 3500-2400 with maxima at 3000(s); 2800(s); 2650(s); 2550(s); 1660(s,broad); 1570(m); 1550(w); 1475(w); 1430(s); 1320(m); 1285(s); 1240(s); 1225(s); 1140(w); 1120(w); 1030(m); 980(m); 840(w); 750(w); 680(m) cm^{-1}.

It was not investigated further.

6.4.0. 3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (LVI,j).

The title hydroxamic acid (1.869 g.) was dissolved in ten per cent sodium hydroxide solution (20 ml.) and heated under reflux for one hour. The reaction mixture was cooled and product A (0.290 g.) precipitated. The filtrate was acidified carefully with concentrated hydrochloric acid and product B (0.950 g.) precipitated. The filtrate from product B was allowed to stand and product C (0.320 g.) precipitated.

None of these products gave a violet color with ethanolic ferric chloride solution.

Product A was dissolved in ethanol, filtered, and reprecipitated with ether to give the sodium salt of α-(o-aminophenylthio)-

acetic acid (LXXXVI) as white crystals, m.p. $> 340^{\circ}$.

Infrared spectrum (KBr disc): 1635(s), 1363(s)(COO^{-}); 3410(s) (NH) cm^{-1}.

Anal.: Calc'd for $C_8H_8NO_2S$ Na: N, 6.83 per cent

Found: N, 6.65 per cent.

The sodium salt was dissolved in a minimum of water, filtered, and acidified with ten per cent hydrochloric acid solution to yield 3,4-dihydro-3-oxo-2H-1,4-benzothiazine(XXXVII) as a white powder, m.p. 171-173°. Lit. (60) m.p. 179°. It had an infrared spectrum identical with that of an authentic sample.

Infrared spectrum (KBr disc): 1661(s)(C=O); 3208(m)(NH) cm^{-1}.

Product B (m.p. $> 340^{\circ}$) was treated with ten per cent sodium hydroxide solution. The insoluble fraction (0.496 g.) was recrystallized from aqueous ethanol to give 2,2'-diaminodiphenyldisulfide (LXXV) as yellow plates, m.p. 90-91°. Lit. (61) m.p. 93-94°. The infrared spectrum was identical with that of the product isolated in section 8.1.9.

Infrared spectrum (KBr disc): 3480(s), 3300(s), 1610(s)(NH_2) cm^{-1}.

The soluble fraction was reprecipitated with concentrated hydrochloric acid as an amorphous yellow powder. (0.225 g.) m.p. $> 300^{\circ}$. It was mostly inorganic.

Infrared spectrum(KBr disc): 3440(s), 1575(s), 1410(m),

1140(s), 1110(m), 1095(m) cm^{-1}.

It was not investigated further.

Product C was recrystallized from aqueous ethanol to give 3,4-dihydro-3-oxo-2H-1,4-benzothiazine (XXXVII) as a white powder, m.p. 170-173°. Lit. (60) m.p. 179°. The infrared spectrum was identical with that of an authentic sample.

7.0.0. Condensation with o-nitrobenzenesulfenyl chloride.

7.1.0. General Method.

o-Nitrobenzenesulfenyl chloride (10 g.) and an excess of the appropriate ketone were dissolved in acetonitrile (100 ml.) and the solution heated under reflux for 2-4.5 hours. Acetonitrile (80 ml.) was then removed by distillation and the reaction mixture cooled to yield the product.

7.1.1. (o-Nitrophenylthio)propan-2-one (LIIIa).

Using general method 7.1.0., the interaction of o-nitrobenzenesulfenyl chloride and acetone (15 g.) for two hours gave the title compound (97 per cent yield) as yellow-brown crystals, m.p. 77-79° (MeOH). Lit. (48) m.p. 81°.

Infrared spectrum (KBr disc): 1715(s)(C=O); 1510(s), 1330(s), 845(m)(NO_2) cm^{-1}.

7.1.2. ω-(o-Nitrophenylthio)acetophenone (LIIIb).

o-Nitrobenzenesulfenyl chloride and acetophenone (15 g.) were interacted for 4.5 hours, using general method 7.1.0., to give the title compound (93 per cent yield) as yellow crystals, m.p. 143-145° (MeOH). Lit. (51) m.p. 147°.

Infrared spectrum (KBr disc): 1685(s)(C=O); 1510(s), 1330(s), 850(m)(NO_2) cm^{-1}.

7.1.3. Ethyl α-benzoyl-α-(o-nitrophenylthio)acetate (LIIId).

o-Nitrobenzenesulfenyl chloride and ethyl α-benzoylacetate (15 g.) were interacted for 2.5 hours, using general method 7.1.0., to give the title compound (95 per cent yield) as yellow crystals, m.p. 120-123° (MeOH). Reported (51) m.p. 123-125°.

Infrared spectrum (KBr disc): 1590(s), 1630(m)(β-ketoester C=O); 1510(s), 1335(s), 845(m)(NO_2) cm^{-1}.

7.1.4. Ethyl α-(o-nitrophenylthio)acetoacetate (LIIIc).

Using general method 7.1.0., o-nitrobenzenesulfenyl chloride and ethylacetoacetate (15 g.) were interacted for 2.25 hours to give the title compound (82 per cent yield) as yellow crystals, m.p. 73-75° (EtOH). Lit. (48) m.p. 74-75°.

Infrared spectrum (KBr disc): 1580(s), 1630(m)(β-ketoester C=O); 1510(s), 1330(s), 848(m)(NO_2) cm^{-1}.

7.1.5. 3-(o-Nitrophenylthio)pentane-2,4-dione (LIIIe).

Using general method 7.1.0., o-nitrobenzenesulfenyl chloride and 2,4-pentanedione (15 g.) were interacted for two hours to give the title compound (88 per cent yield) as yellow crystals, m.p. 141-141.5° (MeOH). Lit. (48) m.p. 136-137°.

Infrared spectrum (KBr disc): 1592(s) (β-diketone C=O); 1515(s), 1335(s), 845(m)(NO_2) cm^{-1}.

7.1.6. α-Aceto-α-(o-nitrophenylthio)acetanilide (LIIIf).

o-Nitrobenzenesulfenyl chloride (0.52 g.) and α-acetoacetanilide (1.05 g.) were dissolved in acetonitrile (20 ml.) and heated under reflux for three hours. The reaction mixture was cooled overnight and product A (0.11 g.) precipitated. The filtrate was evaporated to dryness by flash evaporation to give a semi-solid product. Trituration with ethanol yielded product B (0.43 g.)

Products A and B gave identical infrared spectra. They were combined and recrystallized from ethanol to give the title compound as yellow crystals m.p. 125-126°.

Infrared spectrum (KBr disc): 1575(s)(β-ketoamide); 1515(s), 1330(s)(NO_2); 3333(m)(NH) cm^{-1}.

Anal. $C_{16}H_{14}N_2O_4S$ requires: C, 58.19; H, 4.27; N, 8.48 per cent.

Found: C, 57.71; H, 4.25; N, 8.73 per cent.

7.1.7. α-(o-Nitrophenylthio)-α-cyanoacetamide (LIIIg).

o-Nitrobenzenesulfenyl chloride (0.51 g.) and α-cyanoacetamide (1.03 g.) were dissolved in acetonitrile (20 ml.) and heated under reflux for three hours. The reaction mixture was cooled overnight and α-cyanoacetamide

(0.3 g.) precipitated. The filtrate was evaporated to dryness by flash evaporation to give the title compound (1.11 g.) m.p. 154.5-156° (EtOH).

Infrared spectrum (KBr disc): 1690(s), 1665(s)(C=O); 1525(s), 1345(s), 855(m)(NO_2); 3460(s), 1595(s)(NH_2); 2260(w)(CN) cm^{-1}.

Anal. $C_9H_7N_3O_3S$ requires: C, 45.56; H, 2.97; N, 17.71 per cent.
Found: C, 45.65; H, 3.24; N, 17.70 per cent.

7.1.8. Attempted preparation of (o-nitrophenylthio)nitromethane.

o-Nitrobenzenesulfenyl chloride (5 g.) and nitromethane (10 g.) were dissolved in acetonitrile (50 ml.) and heated under reflux for four hours. Acetonitrile (40 ml.) was removed by distillation and the reaction mixture cooled to yield o-nitrobenzenesulfenyl chloride (3.71 g.). The filtrate was reduced in volume and a product (1.44 g.) precipitated. Crystallization from methanol gave bis(o-nitrophenyl)disulfoxide (LV) as yellow needles m.p. 141.142°. Lit. (62) m.p. 142-143°.

Infrared spectrum (KBr disc): 1050(m)(S=O); 1530(s), 1535(s), 1352(s), 1358(s)(NO_2) cm^{-1}.

Anal. Calc'd. for $C_{12}H_8N_2O_6S_2$: C, 42.35; H, 2.37;
N, 8.23 per cent.

Found: C, 42.77; H, 2.52; N, 8.09 per cent.

8.0.0. Reduction of α-(o-nitrophenylthio)-ketones and ketoesters.

8.1.0. General Method.

A solution of sodium borohydride (0.5 g.) in water (5 ml.) was added to a suspension of palladium (10 per cent)-on-charcoal (0.1 g.)

in water (5 ml.). Dioxane (10 ml.) was added to the mixture and nitrogen gas was bubbled through it (1-2 min.). The (o-nitrophenylthio)-ketone or -ketoester (1.0 g.), dissolved in a minimum of dioxane, was added to the reduction mixture over a period of ten minutes. Nitrogen gas was bubbled through the reaction mixture during the addition of ketone and for an additional 30 minutes.

The reaction mixture was filtered and the filtrate extracted with ether (Ether extract I). The aqueous layer was acidified with concentrated hydrochloric acid, keeping the temperature below 30°, and then extracted with ether (Ether extract II). Ether extracts I and II were then combined and extracted to completion with portions of ten per cent sodium hydroxide solution (Extract A), washed with water, extracted to completion with portions of ten per cent hydrochloric acid solution (Extract B), and washed with water. The ether layer was then dried (Na_2SO_4), and evaporated to yield the neutral fraction.

Basic extract A and its washings were acidified with concentrated hydrochloric acid and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4), and evaporated to yield the acidic fraction.

Acidic extract B and its washings were neutralized with sodium bicarbonate, basified with ten per cent sodium hydroxide solution and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4), and evaporated to yield the basic fraction.

8.1.1. Reduction of (o-nitrophenylthio)propan-2-one (LIIIa).

The title compound (0.983 g.) was reduced using the general method (section 4.8.1.0.) to give a neutral fraction (0.684 g.) and a basic fraction (0.023 g.). No acidic fraction was isolated.

The neutral product, 1-(o-nitrophenylthio)-2-propanol (LVIII) was a yellow oil. This product has a reported (52) b.p. 170° (1.5 mm.).

Infrared spectrum (thin film): 3350(s,broad)(OH); 1510(s), 1335(s), 860(w)(NO_2) cm^{-1}.

The 3,5-dinitrobenzoate, prepared by a conventional method (63) had a m.p. 144.5-146° (EtOH).

Infrared spectrum (KBr disc): 1723(s)(C=O); 1515(s), 1340(s), 860(w)(NO_2) cm^{-1}.

Anal. $C_{16}H_{13}N_3O_8S$ requires: C, 47.17; H, 3.22; N, 10.36 per cent.
Found: C, 47.53; H, 3.57; N, 10.36 per cent.

The basic product was isolated as a brown oil. It had an infrared spectrum identical with that obtained for 1-(o-aminophenylthio)-2-propanol (LIX) prepared as described in section 8.1.4.

8.1.2. Reduction of (o-nitrophenylthio)propan-2-one (LIIIa) with sodium borohydride.

The title compound (0.953 g.) was dissolved in dioxane (15 ml.) and a solution of sodium borohydride (0.5 g.) in water (10 ml.) added.

The solution was allowed to stand at room temperature for one hour, then it was flooded with water, and acidified with concentrated hydrochloric acid, while keeping the temperature below 30°. The solution was extracted with ether, and the ether layer re-extracted successively with ten per cent sodium hydroxide solution, and with ten per cent hydrochloric acid solution, then washed with water, dried (Na_2SO_4), and evaporated to yield 1-(o-nitrophenylthio)-propan-2-ol (LVIII) (0.949 g.) as a yellow oil, the infrared spectrum of which was superimposable upon that of 1-(o-nitrophenylthio)propan-2-ol obtained as described in section 8.1.1.

8.1.3. Reduction of o-(nitrophenylthio)propan-2-one (LIIIa) using excess palladium (ten per cent)-on-charcoal.

The title compound (1.016 g.) was reduced using the general method (section 8.1.0), except that the quantity of palladium(ten per cent)-on-charcoal was increased to 0.5 g. A neutral fraction (0.070 g.) and a basic fraction (0.476 g.) were isolated. No acidic fraction was isolated.

The neutral fraction was isolated as an orange oil. Its infrared spectrum differed from that of 1-(o-nitrophenylthio)propan-2-ol described in section 7.1.1.

Infrared spectrum (thin film): 3380(m,broad), 3050(w), 2960(s), 2920(m), 2855(m), 1585(m), 1480(s), 1455(m), 1445(m), 1415(m), 1370(m), 1340(m), 1290(s), 1255(s), 1155(s), 1115(s), 1110(s),

1030(s), 860(m), 795(s), 755(m), 735(m) cm^{-1}.

It was not investigated further.

The basic fraction was a brown oil. It gave an infrared spectrum similar to, but not identical with 1-(o-aminophenylthio)-propan-2-ol (LIX) prepared as described in section 8.1.4. It gave a red-violet color with two per cent furfural in glacial acetic acid, and reduced Tollen's reagent.

Infrared spectrum (thin film): Broad absorption 3600-3100(OH) with maximum at 3360(s)(NH); 1607(s)(NH) cm^{-1}. Nitro and carbonyl absorption was absent.

Mass spectrum: 201(17), 200(6), 199(44), 186(17), 185(7), 184(46), 183(50), 167(7), 166(13), 165(100), 151(18), 150(96), 149(30), 139(13), 136(15), 125(35), 124(34), 117(31), 109(17), 94(13), 93(13), 91(11), 80(11), 77(13), 74(11), 65(12), 57(10), 45(14), 44(13), 43(10), 41(15), 39(14), 31(21), 29(11), 28(39), 27(11), 18(88), 17(17), m/e (rel.abund. per cent). Numerous peaks of relative abundance less than ten per cent were also present in the mass spectrum.

8.1.4. Preparation of 1-(o-aminophenylthio)propan-2-ol (LIX).

Propylene glycol (6.5 g.) was addeddropwise to a mixture of o-aminothiophenol (12.5 g.) and metallic sodium (0.05 g.) in absolute ethanol (3 ml.) and the reaction mixture heated on a steam bath for 30 minutes. Excess propylene glycol was removed by flash evaporation. Ether was added to the residue and extracted with ten per cent sodium

hydroxide solution, washed with water, dried (Na_2SO_4) and evaporated to yield a yellow oil.

Hydrogen chloride gas was bubbled into a solution of the yellow oil in absolute ethanol/ether. Filtration yielded the hydrochloride salt of o-aminobenzenethiol as a white solid, m.p. 224-225°(d). The filtrate was reduced in volume and a further product precipitated. Crystallization from ethanol/ether yielded the hydrochloride salt of 1-(o-aminophenylthio)propan-2-ol as white crystals m.p. 166-167°(d). Lit. (52) m.p. 159-160°(d).

Infrared spectrum (KBr disc): 3260(m)(OH); 2390(w) 2420(w), 2480(w) 2550(m), 1950(w,broad) (NH_3^+)(ref. 59) cm^{-1}.

The hydrochloride salt of 1-(aminophenylthio)propan-2-ol was dissolved in a minimum of water and basified with five per cent sodium bicarbonate solution. The solution was extracted with ether; the ether layer washed with water, dried (Na_2SO_4) and evaporated to yield 1-(o-aminophenylthio)propan-2-ol (LIX) as a yellow oil. This product is reported in literature (52) an oil, b.p. $1.5^{140°}$.

Infrared spectrum (thin film): 3580-3100(OH) with maximum at 3350(s)(NH_2), 1608(s)(NH_2) cm^{-1}.

Mol. weight: Calc'd for $C_9H_{13}NOS$: 183

Found (mass spectrum): 183.

8.1.5. Reduction of ω-(o-nitrophenylthio)acetophenone (LIIIb).

The title compound (0.938 g.) was reduced using the general method (section 8.1.0.) to give a neutral fraction (0.863 g.) and a

basic fraction (0.008 g.).

No acidic fraction was isolated.

The neutral product, 2-(o-nitrophenylthio)-1-phenylethanol (LXVI), was isolated as an orange oil, which, on standing, slowly solidified to a yellow solid, m.p. 98-99°. Lit. (51) m.p. 97-98°.

Infrared spectrum (KBr disc): 3300(s,broad)(OH); 1505(s), 1335(s), 840(m)(NO_2) cm^{-1}.

The p-nitrobenzoate, prepared in the conventional manner (63), had a m.p. 139-141°(EtOH).

Infrared spectrum (KBr disc): 1732(s)(C=O); 1525(s); 1340(s), 870 or 850(w)(NO_2) cm^{-1}.

Anal. $C_{21}H_{16}N_2O_6S$ requires: C, 59.42; H, 3.80; N, 6.60 per cent.
Found: C, 59.58; H, 4.21; N, 6.67 per cent.

The basic product was a brown oil. It had an infrared spectrum identical with that of 2-(o-aminophenylthio)-1-phenylethanol (LXVII) obtained as described in section 8.1.6.

8.1.6. Reduction of ω-(o-nitrophenylthio)acetophenone (LIIIb) using excess palladium (ten per cent)-on-charcoal.

The title compound (10.03 g.) was reduced using the general method (section 8.1.0.), except that the quantity of palladium(ten per cent)-on-charcoal was increased to 2.638 g. A neutral fraction (3.832 g.) and a basic fraction (4.079 g.) were isolated. The acidic

fraction isolated (0.736 g.) was starting material.

The neutral product was an orange-red oil, the infrared spectrum of which differed from that obtained for 2-(o-nitrophenylthio)-1-phenylethanol (LXVI), isolated as described in section 3.1.5. Thin layer chromatography on silica gel using benzene:petroleum ether: ethanol (5 :50:5) as solvent gave three spots, rf values 7.2, 5.5, and 3.1. Column chromatography on a neutral alumina column 1.1 x 15 cm. with petroleum ether as solvent yielded one component (neutral component A), which moved ahead of the remainder of the mixture. Elution with six per cent ethanol in benzene yielded the remainder of the mixture, which was rechromatographed on a neutral alumina column (2.2 x 15 cm.). Neutral component B was the first band eluted with benzene as solvent. The remainder of the mixture was washed off the column using ethanol. From this latter mixture of neutral components, fraction C (rf 5.9) separated on silica gel plates using five per cent ethanol in benzene as solvent.

Neutral component A (0.306 g.) was a bright orange solid. Crystallization from acetone gave 2,2'-bis(3-phenyl-2H-1,4-benzothiazine) (LXVIII) as small, orange needles, m.p. 243-243.5°. Lit. (55) m.p. 234-236°.

Infrared spectrum (KBr disc): Major peaks at 1445, 750, 680 cm^{-1}. Carbonyl and nitro absorption peaks were absent.

Anal. $C_{28}H_{20}N_2S_2$ requires: C, 74.96; H, 4.49; N, 6.24 per cent. Mol. weight 448.

Found: C, 74.80; H, 4.94; N, 6.35 per cent.

Mass spectrum: 450(0.7), 449(3), 448(11), 447(29), 446(80), 445(13), 413(11), 369(10), 342(13), 325(12), 235(11), 225(32), 224(100), 223(28), 211(13), 121(23), 77(14), 76(10), 52(15), 51(14), 39(16), m/e (rel.abund. per cent). Numerous other peaks of rel.abund. less than ten per cent were also present in the spectrum.

Neutral component B was a viscous orange-yellow oil.

Infrared spectrum (thin film): 3600(m,broad), 3100(m), 3063(s), 3040(s), 2963(m), 2930(m), 2890(m), 2875(m), 1970(w), 1895(w), 1832(w), 1735(w,broad), 1575(s), 1540(s), 1495(s), 1480(s), 1455(s), 1380(m), 1335(m), 1320(s), 1305(s), 1290(s), 1260(s), 1230(m), 1205(s), 1180(m), 1160(m), 1130(m), 1098(s), 1060(s), 1030(s), 1000(m), 990(m), 940(w), 920(m), 885(s), 850(m), 835(m), 810(m), 755(s), 720(s), 695(s), 670(s) cm^{-1}.

It was not investigated further.

Neutral component C was also a viscous yellow oil.

Infrared spectrum (thin film): 3600-3200(s), 3060(w), 3030(w), 2970(w), 2920(w), 1590(m), 1565(w), 1510(m), 1505(m), 1490(m), 1470(s), 1450(s), 1330(m), 1300(m), 1245(m), 1190(w), 1100(m), 1050(s), 995(w), 980(w), 905(w), 840(w), 750(s), 720(s), 710(s), 690(s) cm^{-1}.

Mass spectrum: 281(0.8), 278(1.4), 265(6.3), 264(1.6), 263(10), 150(9), 149(100), 78(40), 77(21), 74(22), 59(28), 57(20), 45(18), 41(12), 31(37), 29(25), m/e (rel.abund. per cent). Numerous other

peaks of rel.abund. less than ten per cent were also present in the spectrum.

It was not investigated further.

The basic fraction was a brown oil. It gave a red-violet color with two per cent furfural in glacial acetic acid solution. Addition of ten per cent hydrochloric acid solution to a solution of the oil in ether precipitated 2-(o-aminophenylthio)-1-phenylethanol hydrochloride as fine white crystals, m.p. 180-181°(acetone/n-hexane). Lit. (52) m.p. 172°.

Infrared spectrum (KBr disc): 3420(s)(OH); 2550(m), 2600(m) (N^+-H)(ref.59) cm^{-1}.

Anal. Calc'd. for $C_{14}H_{16}ClNOS$: C, 59.67; H, 5.72; N, 4.97 per cent.

Found: C, 60.08; H, 6.03; N, 5.12 per cent.

The hydrochloride salt was dissolved in a minimum of ethanol, ten per cent hydrochloric acid solution (2 ml.) added, and the solution basified with ten per cent bicarbonate solution. The basic solution was then extracted with ether, the ether layer washed with water, dried (Na_2SO_4), and evaporated to yield 2-(o-aminophenylthio)-1-phenylethanol (LXVII) as an oil. This product is described in literature (52) as an oil b1.5 192° which forms a solid, m.p. 57-8°.

Infrared spectrum (thin film): 3600-3140(s,broad)(OH) with maxima at 3360(s), 3460(s)(NH_2); 1610(s)(NH_2) cm^{-1}.

Mol.weight: Calc'd. for $C_{14}H_{15}NOS$: 245

Found(mass spectrum): 245.

8.1.7. Reduction of ethyl α-benzoyl-α-(o-nitrophenylthio)acetate (LIIId).

The title compound (1.932 g.) was reduced using general method 8.1.0. and gave a neutral product (0.321 g.), an acidic product (0.914 g.), and a basic product (0.175 g.).

The acidic product was a viscous brown oil and was 1-(3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)benzyl alchohol (LXXV). This product is reported (51) to be a viscous yellow oil. It gave a violet color with ethanolic ferric chloride solution. Its infrared spectrum was identical with that of an authentic sample (51).

Infrared spectrum (thin film): 1690(s,broad)(hydroxamate C=O); 3600-2700(s)(hydrogen bonded OH) cm^{-1}.

The ferric chelate of this hydroxamic acid was prepared by dissolving the oil (100 mg.) in a minimum of ethanol, adding excess ethanolic ferric chloride solution, and flooding the mixture with water. This yielded the chelate as a purple-brown powder.

Infrared spectrum (KBr disc): 3450(s,broad)(OH); 1528(s) (chelated carbonyl)(ref. 50) cm^{-1}.

The ferrous chelate was prepared by the reported method (51), it melted at 139-145°. Reported (51) m.p. 140-145°.

The neutral fraction was isolated as a viscous oil. Its in-

frared spectrum was not the same as that of 2-(o-nitrophenylthio)-1-phenylethanol (LXVII), obtained as described in section 8.1.8.

Infrared spectrum (thin film): 3400(s,broad), 3070(m), 3040(m), 2980(m), 2920(m), 2860(w), 1730(s), 1675(s), 1590(s), 1570(m), 1515(s), 1495(s), 1485(s), 1455(s), 1370(s), 1340(s), 1300(s), 1260(s), 1150(s), 1110(s), 1060(s), 1020(s), 850(w), 800(m), 750(s), 730(s), 695(s) cm^{-1}.

It was not investigated further.

The basic product, isolated as a viscous brown oil, gave a red-violet color with two per cent furfural in glacial acetic acid solution. Its infrared spectrum was superimposable upon that of 2-(o-aminophenylthio)-1-phenylethanol (LXVII), obtained as described in section 8.1.6.

8.1.8. Reduction of ethyl α-benzoyl-α-(o-nitrophenylthio)acetate (LIIId) with sodium borohydride.

The title compound (0.523 g.) was dissolved in dioxane (20 ml.). A solution of sodium borohydride (0.286 g.) in water (10 ml.) was added and the mixture allowed to stand at room temperature for one hour. It was flooded with water and 2-(o-nitrophenylthio)-1-phenylethanol (LXVI) (0.195 g.) precipitated as yellow crystals, m.p. 99-100.5°(EtOH) Lit. (51) m.p. 97-98°. The mother liquor was extracted with ether. The ether solution was re-extracted successively with ten per cent sodium hydroxide solution, with ten per cent hydrochloric acid solution, and with water. It was dried and evaporated to yield a further quantity

of 2-(o-nitrophenylthio)-1-phenylethanol (0.304 g.) as a yellow oil which slowly solidified to yellow crystals, m.p. 96-98° on standing. The infrared spectra of both samples were identical, and superimposable upon that of 2-(o-aminophenylthio)-1-phenylethanol obtained as described in section 8.1.5.

8.1.9. Reduction of ethyl α-benzoyl-α-(o-nitrophenylthio)acetate (LIIId) using excess palladium(ten per cent)-on-charcoal.

The title compound (4.98 g.) was reduced using general method 8.1.0., except that the quantity of palladium (ten per cent)-on-charcoal was increased to 1.24 g. The neutral fraction (2.03 g.) (Product A) and the acidic product (0.690 g.) (Product B) were isolated as described in the general method (Section 8.1.0.). An additional product (1.03 g.) (Product C) precipitated from the hydrochloric acid extract before its basification. It was removed, and the filtrate was basified and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4), and evaporated to yield basic material (0.746 g.)(Product D.)

Product A was isolated as a viscous orange oil. Thin layer chromatography on silica gel using benzene:petroleum ether:ethanol (50:50:5) as solvent gave four major spots. The mixture was chromatographed on a neutral alumina column 2.2 x 15 cm. Elution with petroleum ether:benzene(1:1) gave four bands, the first one of which separated readily from the other three. This fraction was a bright

orange oil, which is tentatively identified as 2-phenylbenzothiazole N-oxide (LXXII).

Infrared spectrum (thin film): 3060(w), 2960(s), 2930(s), 2860(s), 1740(w), 1600(w), 1570(w), 1550(w), 1485(m), 1465(m), 1445(s), 1448(s), 1388(m), 1340(w), 1320(m), 1305(m), 1260(s), 1220(w), 1090(s), 1070(s), 1020(s), 960(w), 940(w), 840(w), 795(s), 760(s), 745(m), 720(w), 680(m), cm^{-1}.

Mass spectrum: 229(0.5), 228(1.7), 227(9), 213(7), 212(22), 211(100), 210(16), 111(11), 108(20), 97(16), 95(10), 85(17), 83(17), 81(11), 78(19), 71(26), 69(20), 57(41), 55(25), 43(30), 41(16), m/e (rel. abund. per cent). Numerous other peaks with rel.abund. less than ten per cent were also present in the spectrum.

The other fractions could not be separated.

Product B, 1-(3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)benzyl alcohol (LXX), was isolated as a viscous brown oil, which gave an infrared spectrum identical to that obtained for the hydroxamic acid described in section 8.1.7. It gave a violet color with ethanolic ferric chloride solution.

Recrystallization of product C from ethanol/ether gave the dihydrochloride salt of 2,2'-diaminodiphenyl disulfide (LXXV), m.p. 220.5-222°. Lit. (61) m.p. 210-211°. The infrared spectrum was identical with that of the product obtained by bubbling hydrogen

chloride gas into a solution of 2,2'-diaminodiphenyl disulfide in anhydrous ether.

Infrared spectrum (KBr disc): 2860(s,broad), 2595(s), 1900(w, broad)(NH_3^+) cm^{-1}.

The salt was dissolved in a minimum of ethanol and the solution basified with four drops of ten per cent sodium hydroxide solution. Sufficient water was added to cloud the solution and 2,2'-diaminodiphenyldisulfide precipitated as yellow plates, m.p. 91-92°. Lit. (61) m.p. 93-94°.

Infrared spectrum (KBr disc): 3480(s), 3300(s), 1610(s)(NH_2) cm^{-1}.

Mol.weight: Calc'd for $C_{12}H_{12}N_2S_2$:248
Found (mass spectrum):248.

Product D, isolated as a brown oil, gave an infrared spectrum identical with that of 2-(o-aminophenylthio)-1-phenylethanol (LXVII), obtained as described in section 8.1.5.

8.1.10. Reduction of ethyl α-(o-nitrophenylthio)acetoacetate (LIIIc) using excess palladium(ten per cent)-on-charcoal.

The title compound (1.401 g.) was reduced using general method 8.1.0., except that the quantity of palladium (ten per cent)-on-charcoal was increased to 0.33 g. Product A (0.052 g.) precipitated from the basic reaction mixture after filtering off the catalyst. Treat-

ment of the subsequent filtrate as described in the general method yielded a neutral fraction (0.196 g.), an acidic fraction (0.276 g.) and a basic fraction (0.200 g.).

Product A was recrystallized from aqueous ethanol to give ethyl-3-methyl-4H-1,4-benzothiazine-2-carboxylate (LXXVI) as yellow crystals, m.p. 144-146°. Lit. (64) m.p. 144-145°.

Infrared spectrum (CCl_4): 1701(s)(α,β-unsat^d C=O); 3430(m) (NH) cm^{-1}.

NMR:(in $CDCl_3$): 8.72 (3H, triplet, J=7 cps)($COOCH_2\underline{CH_3}$); 7.72 (3H, singlet)($C=\underline{CH_3}$); 5.83 (2H, quartet, J=7 cps)($COO\underline{CH_2}CH_3$); 3.08-3.78 (4H, multiplet)(ring protons); 4.17 (1H, broad, exchanged in D_2O)(NH).

The acidic fraction was presumed to be 2-(3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)ethanol (LXXVIII). It was a viscous brown oil which gave a violet color with ethanolic ferric chloride solution. This product is reported (51) as a viscous yellow oil.

Infrared spectrum (thin film): 1710(s), 1665(s)(C=O); 3660-2300(s)(hydrogen-bonded OH) cm^{-1}.

The neutral and basic fractions were viscous oils which were not investigated further.

8.1.11. Reduction of ethyl α-(o-nitrophenylthio)acetoacetate (LIIIc) using zinc and ammonium chloride.

A solution of ammonium chloride (1 g.) and water (10 ml.) was added to a solution of the title compound (1 g.) in ethanol (50 ml.). The mixture was stirred and zinc dust (1 g.) was added in small portions over a period of 30 minutes. The mixture was stirred for an additional hour, filtered, and the residual zinc washed with 40 ml. of water. Ethanol (40 ml.) was removed by distillation and the mixture cooled to yield a yellow precipitate, (0.3 g.) which was removed. The filtrate was allowed to stand overnight and additional precipitate (0.1 g.) was obtained. The two precipitates were combined and recrystallized from aqueous ethanol to give ethyl 3-methyl-4H-1,4-benzothiazine-2-carboxylate (LXXVI) as yellow crystals, m.p. 144-146°. Lit. (64) m.p. 144-145°.

Infrared spectrum (CCl_4): 1701(s)(α,β-unsat^d C=O); 3430(m)(NH) cm^{-1}.

9.0.0. Preparation of (6-chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetohydroxamic acid (LVII).

A solution of hydroxylamine hydrochloride (2.5 g.) in hot methanol (20 ml.) was added to a solution of potassium hydroxide (8 g.) in hot methanol (30 ml.), and the mixture allowed to stand in an ice bath for five minutes.

A solution of methyl (6-chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIi) (4.04 g.) in hot methanol (50 ml.)

was added to the above mixture and the solution filtered immediately. The filtrate was allowed to stand at room temperature for three days, then it was filtered to yield the potassium salt of the title compound (2.95 g.). This was dissolved in a minimum of hot ten per cent acetic acid. When this solution was filtered and cooled it yielded the title compound as white crystals, m.p. 187.5-188.5° (EtOH).

Infrared spectrum (KBr disc): 1640(s), 1665(s)(hydroxamate C=O); 3270(s)(NH); 3200(s,broad)(OH) cm^{-1}.

Anal.: $C_{10}H_9ClN_2O_4S$ requires: C, 41.60; H, 3.14, N, 9.70 per cent.

Found: C, 41.82; H, 3.17; N, 9.45 per cent.

10.0.0. Xanthenyl derivatives of 2H-1,4-benzothiazine hydroxamic acids.

10.1.0. 3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (LVIj).

Xanthydrol (0.7 g.) was stirred in glacial acetic acid (3 ml.) until solubilization was almost complete. 3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (0.5 g.) was added to the solution and the mixture stirred for 15 minutes. The product which precipitated (0.25 g.) was collected by filtration and recrystallized from acetone to give 3,4-dihydro-3-oxo-4-(9-xanthenyloxy)-2H-1,4-benzothiazine as white crystals (LXXXVII a) m.p. 157.5-159°.

Infrared spectrum (KBr disc): 1691(s)(C=O) cm^{-1}.

Anal. $C_{21}H_{15}NO_3S$ requires: C, 69.79; H, 4.18; N, 3.88 per cent.

Found: C, 69.46; H, 4.15; N, 3.69 per cent.

10.2.0. 3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (LVIk).

Xanthydrol (0.5 g.) was stirred in glacial acetic acid (3 ml.) until solubilization was almost complete. 3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine 1,1-dioxide (0.3 g.) was dissolved in glacial acetic acid (1 ml.) with the aid of heat and added to the above solution. The mixture was stirred for 15 minutes. What was assumed to be 3,4-dihydro-3-oxo-4-(9-xantheryloxy)-2H-1,4-benzothiazine 1,1-dioxide (LXXXVII b) precipitated and was collected by filtration (0.475 g.) m.p. 166-168°. Attempts to recrystallize this compound resulted in decomposition.

Infrared spectrum (KBr disc): 1698(s)(C=O) cm^{-1}.

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SUMMARY

1) The following esters were prepared by the action of o-chloro- or o-bromonitrobenzenes on α-mercaptoacids, followed by esterification:

a) Dimethyl α-(o-nitrophenylthio)succinate (LIg).

b) Dimethyl α-(4-methyl-2-nitrophenylthio)succinate (LIi).

c) Dimethyl α-(4-bromo-2-nitrophenylthio)succinate (LIh).

d) Dimethyl α-(4-trifluoromethyl-2-nitrophenylthio)succinate (LIj).

e) Dimethyl α-(4-chloro-2-nitrophenylthio)succinate (LIk).

f) Methyl α-(o-nitrophenylthio)acetate (LIm).

2) Action of o-nitrobenzenesulfenyl chloride on ketones, ketoesters and nitromethane yielded these compounds:

a) (o-Nitrophenylthio)propan-2-one (LIIIa).

b) ω-(o-Nitrophenylthio)acetophenone (LIIIb).

c) Ethyl α-benzoyl-α-(o-nitrophenylthio)acetate (LIIId).

d) Ethyl α-(o-nitrophenylthio)acetoacetate (LIIIc).

e) 3-(o-Nitrophenylthio)pentane-2,4-dione (LIIIe).

f) α-Aceto-α-(o-nitrophenylthio)acetanilide (LIIIf).

g) α-(o-Nitrophenylthio)-α-cyanoacetamide (LIIIg).

h) Bis(o-nitrophenyl)disulfoxide (LV).

3) These hydroxamic acids were prepared by reduction of (o-nitrophenylthio)acetates using sodium borohydride and palladium-charcoal:

a) (3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic

acid (LVIb).

b) (6-Methyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)-acetic acid (LVId).

c) Methyl (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIe).

d) (6-Trifluorimethyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIh).

e) Methyl (6-chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate (LVIi).

f) 3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine (LVIj).

4) (6-Chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetohydroxamic acid (LVII) was prepared by the action of hydroxylamine hydrochloride on methyl (6-chloro-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate.

5) The following compounds were obtained by the reduction of (o-nitrophenylthio)propan-2-one with sodium borohydride and palladium-charcoal:

a) 1-(o-Nitrophenylthio)propan-2-ol (LVIII).

b) 1-(o-Aminophenylthio)propan-2-ol (LIX).

c) 7-Chloro-3,4-dihydro-3-methyl-2H-1,4-benzothiazine (LXI).

d) 3,4-Dihydro-3-methyl-2H-1,4-benzothiazine (LXII).

6) The reduction of ω-(o-nitrophenylthio)acetophenone using

sodium borohydride and palladium-charcoal yielded the following compounds:

a) 2-(Nitrophenylthio)-1-phenylethanol (LXVI).

b) 2-(o-Aminophenylthio)-1-phenylethanol (LXVII).

c) Bis[2-(3-phenyl-2H-1,4-benzothiazine)] (LXVIII).

7) 2-(o-Nitrophenylthio)-1-phenylethanol (LXVI) was obtained from the reduction of ethyl α-benzoyl-α-(o-nitrophenylthio)acetate using sodium borohydride.

8) Reduction of ethyl α-benzoyl-α-(o-nitrophenylthio)acetate with sodium borohydride and palladium-charcoal yielded the following products:

a) 1-(3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)-benzyl alcohol (LXXX).

b) 2-(o-Aminophenylthio)-1-phenylethanol (LXVII).

c) 2-Phenylbenzothiazole N-oxide (LXXII).

d) Hydrochloride salt of 2,2'-diaminodiphenyldisulfide (LXXV).

9) The compounds were obtained from the reduction of ethyl α-(o-nitrophenylthio)acetoacetate using sodium borohydride and palladium-charcoal:

a) Ethyl 3-methyl-4H-1,4-benzothiazine-2-carboxylate (LXXVI).

b) 2-(3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)ethanol (LXXXVIII).

10) 3,4-Dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine, when treated with aqueous hydrochloric acid, yielded the following compounds:

a) 7-Chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (LXXX).

b) 3,4-Dihydro-3-oxo-2H-1,4-benzothiazine (XXXVII).

11) The following compounds were obtained when Methyl (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate was treated with aqueous hydrochloric acid:

a) (6-Bromo-7-chloro-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)-acetic acid (LXXXII).

b) (6-Bromo-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXI).

12) Action of aqueous sodium hydroxide on methyl (6-bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetate yielded the following compounds:

a) (6-Bromo-3,4-dihydro-4-hydroxy-3-oxo-2H-1-4-benzothiazin-2-yl)-acetic acid (LVIf).

b) (6-Bromo-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXI).

c) 6-Bromo-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetic acid (LXXXV).

13) Treatment of (3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid with aqueous sodium hydroxide yielded these compounds:

a) (3,4-Dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (XXXVIIb).

b) 3,4-Dihydro-3-oxo-2H-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetic acid (XXXVIIc).

14) (6-Methyl-3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid, when treated with aqueous sodium hydroxide, yielded the following products:

a) (6-Methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazin-2-yl)acetic acid (LXXXIII).

b) (6-Methyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine-$\Delta^{2,\alpha}$-acetic acid (LXXXIV).

15) The following compounds were obtained when 3,4-dihydro-4-hydroxy-3-oxo-2H-1,4-benzothiazine was treated with aqueous sodium hydroxide:

a) Sodium salt of (o-aminophenylthio)acetic acid (LXXXVI)

b) 3,4-Dihydro-3-oxo-2H-1,4-benzothiazine (XXXVII).

c) 2,2'-Diaminodiphenyldisulfide (LXXV).

16) When benzothiazine hydroxamic acids were treated with xanthydrol, the following products resulted:

a) 3,4-Dihydro-3-oxo-4-(9-xanthenyloxy)-2H-1,4-benzothiazine (LXXXVIIa).

b) 3,4-Dihydro-3-oxo-4-(9-xanthenyloxy)-2H-1,4-benzothiazine 1,1-dioxide (LXXXVIIb).